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UPTAKE OF RADIOACTIVE IODINE IN THE THYROID OF PATIENTS WITH IMPAIRED LIVER FUNCTION*

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THIS publication concerns a group of patients with hepatic insufficiency in which a substantial number of the individuals studied had increased uptake of I^{131} by the thyroid gland. In the beginning, elevated I^{131} thyroidal uptakes were noted in a number of patients with concomitant liver disease. These unexplained elevations prompted the study of the possible relationship between liver function and iodine uptake by the thyroid. Accordingly, all patients in this series were selected on the basis of two criteria: 1) definite evidence of hepatic insufficiency, and 2) no gross evidence of thyroid disease. Some preliminary observations have been made on the mechanism of the high uptake of radioiodine in these patients.

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METHODS

The study is based on a total of 50 patients—47 with Laennec's cirrhosis,[1] 2 with cardiac cirrhosis and 1 with acute infectious hepatitis. Twenty-six were males and 24 were females. For the principal part of this investigation all patients were studied on the hospital wards. Many had records of multiple admissions to the hospital with a diagnosis of cirrhosis and, in most instances, there was a history of excessive consumption of alcoholic beverages. Special attention was given to the presence of certain physical findings, such as spider angiomata, jaundice, size and contour of the liver, and evidences of portal hypertension. The presence or absence of ascites was noted, and care was taken to determine whether it was increasing, decreasing, or stationary at the time the I^{131} studies were made. Evidence for portal hypertension was based on visible abdominal veins, roentgenologic evidence of esophageal varices, and a history of gastrointestinal hemorrhage.

Routine laboratory determinations for a measure of the function of the liver included bromsulphalein® retention, cholesterol and cholesterol esters, icterus index, bilirubin (Van den Bergh), serum alkaline phosphatase, cephalin flocculation, thymol turbidity, total serum proteins, serum albumin and globulin fractions, prothrombin time, and blood urea nitrogen.

Liver biopsies were carried out on 21 patients in this series. In 20 the specimens were procured within six weeks of a radioactive iodine uptake test. This not only assisted in confirming the diagnosis of liver disease, but also reflected the character of the damage of the liver.

The character of the thyroid was carefully evaluated by at least two of the authors. Any patient who had a palpable mass, enlargement or firmness of the thyroid was excluded from this study. Basal metabolic rate (BMR) determinations were procured on most patients. Although many of these rates were normal, the validity of the elevated values as a reflection of thyroid activity was open to question because of the physical and emotional instability which abstinence from alcohol may have produced.

Radioiodine uptakes by the thyroid were determined on all of the patients in this series. In 12 instances a subsequent I^{131} uptake test was made after the clinical status of the patient had changed. Fifty presumably normal individuals served as controls for I^{131} uptakes. The results of these observations were compared with the uptakes observed in patients with disease of the liver (Fig. 1).

The standard routine of this laboratory was followed for the I^{131} thyroidal uptake, according to the method of Skanse (1). A dose of 25 microcuries of I^{131}, with 10 micrograms of sodium iodide as carrier, was given by mouth. An identical dose of I^{131} in a 100-ml. volumetric flask was preserved as a standard for each patient. After forty-eight hours the thyroid area was counted according to the method described by Skanse. The result was compared to the standard count, and the uptake by the thyroid was recorded as a percentage of the original dose. The measurements were made with a scintillation

[1] Included in this category is 1 patient who had hemochromatosis and 2 patients in whom the liver, on the basis of marked fatty metamorphosis, was regarded as being in an early phase of cirrhosis.

counter in a lead shield, so that only the neck of the patient was counted. This apparatus was originally standardized by using it in patients who, on the same day, were also counted by Skanse's instrument and with the geometry originally used by him (1). In the authors' laboratory, an uptake of 50 per cent or higher is almost always associated with symptoms of thyrotoxicosis.

In a few instances the rate of accumulation of I^{131} by the thyroid and the renal excretion rate of I^{131} were determined according to the method of Keating *et al.* (2).

The level of serum protein-bound iodine was determined in 6 patients who had an I^{131} thyroidal uptake of 50 per cent or more.[2]

In this series of patients there were 17 deaths. In 5 of these a postmortem examination was made. Special attention was directed to the status of the liver, thyroid and kidney. Mean cell-height determinations were made on the thyroidal epithelium by measuring a representative cell of each of 100 acini with an ocular micrometer while the cells were observed under oil immersion, according to the method used on the thyroid of chicks by Rawson and Salter (3).

RESULTS

The radioiodine uptake by the thyroid was found to be 50 per cent or higher in 20 out of the 50 patients[3] in this study. The distribution of the I^{131} among the 50 patients is compared to the distribution among 50 normal subjects in Figure 1.

In spite of the high incidence of elevated thyroidal I^{131} uptakes in this series of patients, clinical evidence of thyrotoxicosis, such as goiter, eye signs or warm moist skin, was absent. However, many had lost weight and exhibited a coarse tremor associated with abstinence from alcohol. Satisfactory BMR determinations were obtained in 13 of the patients who had an I^{131} uptake of 50 per cent or more; in 9 of these a BMR of +10 per cent or less was found, and in only 4 were there varying degrees of elevation above normal. Five of the patients with a normal BMR had no demonstrable ascites, a factor which might result in falsely low values.

It has been pointed out that the criteria for choosing these patients were the clinical and laboratory evidences of moderate and severe disease of the liver. The results of cephalin flocculation and thymol turbidity tests were normal in 5 out of 49 of the patients and slightly abnormal in 7 out of 49. In the remaining 38 patients these tests indicated severe damage to the liver. The serum cholesterol levels were found to be 140 mg. per 100 ml. or higher in 19 out of 48 of the patients, between 140 and 100 mg. in 12, and below 100 mg. in 17. The bromsulphalein® retention was 16 per cent or higher in 34 out of 38 of the patients tested.

[2] The authors wish to thank Dr. Reginald Shipley, Crile Veterans Administration Hospital, for these determinations.

[3] There were among these patients a few with abnormally low uptakes, which are usually the result of a recent iodine intake. In some instances such a source of error was found and was the basis for excluding the case from the series. No known cause could be determined for the abnormally low values appearing in Figure 1.

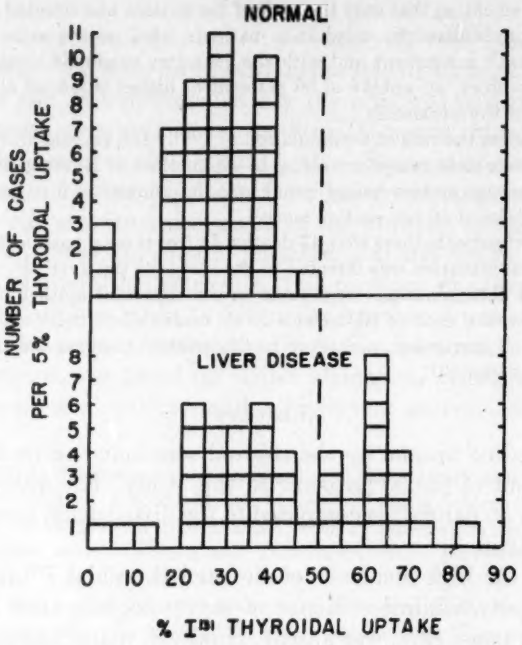

FIG. 1. The distribution of I^{131} thyroidal uptakes in 50 normal subjects and 50 patients with disease of the liver.

Forty per cent of the patients with disease of the liver had uptakes of 50 per cent or higher.

On the basis of gastrointestinal bleeding, x-ray evidence of esophageal varices, or demonstrable epigastric veins, portal hypertension was present in 37 out of 50 of the patients.

During the course of the study the clinical impression was gained that those patients with the most extreme evidence of liver failure could be expected to have an abnormally high I^{131} thyroidal uptake. This hypothesis was tested by a numerical system of evaluation in which the various laboratory and clinical findings of liver disease were given individual arbitrary values, graded according to their degree of severity. In each case the sum total of these values reflected the relative degree of damage to the liver. In the system used, the correlation between these total values and the I^{131} thyroidal uptake was inconclusive. On further analysis, however, some of the individual clinical features seemed to have significant relationship to the I^{131} uptake.

Spider angiomata were found in 20 out of 39 white patients.[4] Table 1

[4] The occurrence of spider angiomata was considered only in the white patients because of the difficulty of identifying these lesions in the negro.

shows that in the group of patients with an elevated I^{131} thyroidal uptake, spider angiomata were encountered approximately twice as often as they were in the group of patients with a normal uptake. Subsequent observations in many of these patients revealed a reduction in the I^{131} thyroidal uptake coincident with other signs of clinical improvement, including the fading or disappearance of spider angiomata.

For the purpose of this study, jaundice was graded on a basis from I to III, designating III as the most severe (see legend to Figure 2). It will be seen in Figure 2 that most of the patients with high I^{131} thyroidal uptakes had jaundice graded II or III. Among the patients with high I^{131} thyroidal uptakes, but without jaundice, 2 of 4 patients were found to have an ele-

TABLE 1. RELATIONSHIP OF I^{131} THYROIDAL UPTAKE TO THE PRESENCE OF SPIDER ANGIOMATA IN WHITE PATIENTS

	Uptake of I^{131} by thyroid	
	Below 50 per cent	50 per cent or more
Patients with spider angiomata	8	12
Total number of patients	22	17

vated blood urea nitrogen level at the time of the uptake tests, a finding which suggested that impaired renal excretion in these 2 patients may have influenced the I^{131} thyroidal uptake.

A microscopic study was made on specimens of liver obtained from 25 patients by biopsy or postmortem examination. In all but 1 of these the tissue was obtained within six weeks of the date of the I^{131} thyroidal uptake test. The tissue was fixed in formalin-Zenker's and stained in hematoxylin and eosin. These livers showed a broad spectrum of damage, ranging from acute necrosis to extensive connective tissue replacement and nodular regeneration. Two types of cellular damage were observed: 1) fatty metamorphosis, and 2) varying degrees of vacuolation of the cytoplasm. These two changes were graded independently from I to III, where III represented extreme fatty metamorphosis and heavily vacuolated cytoplasm to the extent of apparent disintegration of the cell. Since similar values were usually found for these two features in any one liver, a corresponding value was assigned to that particular liver. There was no correlation between the I^{131} thyroidal uptake and the presence of connective tissue or nodularity; however, among the group of patients with the most severe cellular damage in the liver there appeared to be a significant number with increased thyroidal uptakes (Fig. 3).

The I^{131} of the ascitic fluid is known to reach an equilibrium with that of

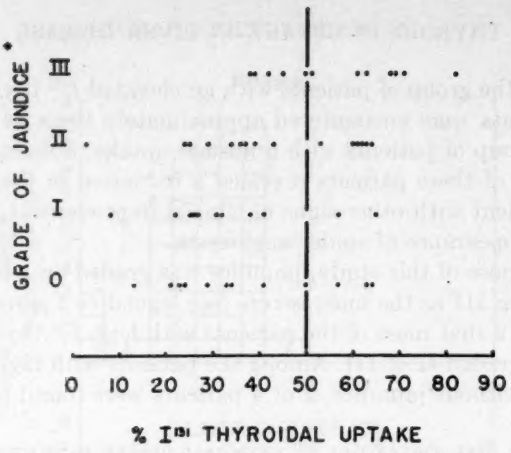

FIG. 2. The relationship of jaundice to the I^{131} thyroidal uptake.

*=Grade I denotes subclinical jaundice identified by an icterus index of 10 to 20 or a total bilirubin level (Van den Bergh) of 1.0 to 2.0 mg. per 100 ml. Grade II jaundice was identified by the presence of mild clinical icterus, an icterus index of 20 to 40, or a total bilirubin level of 2.0 to 4.0 mg. per 100 ml. Grade III jaundice was identified by the presence of deep clinical icterus, an icterus index higher than 40, or a total bilirubin level of 4.0 mg. per 100 ml. or higher.

Among the patients with elevated I^{131} thyroidal uptakes there were 3 who had an elevated concentration of blood urea nitrogen. Attention is drawn to these, because 2 of the 3 increases occurred in the group graded 0 jaundice (thyroidal uptakes, 63 and 57 per cent). The other increase occurred in the group graded II (uptake, 53 per cent).

One patient with Grade III jaundice had infectious hepatitis and a 45 per cent thyroidal uptake. A second patient with Grade II jaundice had cardiac cirrhosis and an uptake of 60 per cent. One patient with Grade I jaundice had cardiac cirrhosis and an uptake of 31 per cent. All other patients in this chart had Laennec's cirrhosis.

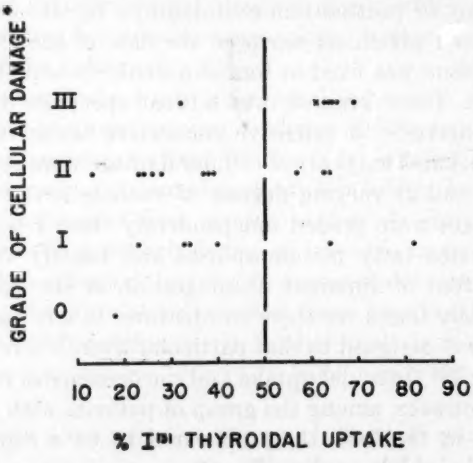

FIG. 3. The relationship of I^{131} thyroidal uptake and the degree of cellular damage observed in the liver.

See next page for explanation.

the serum (4). Therefore the possible relationship of ascites to high I^{131} thyroidal uptake was considered. The ascites in these patients was classified as present or absent; and, if present, whether stationary, increasing or decreasing. No significant correlation was demonstrable between the status of the ascites and the I^{131} thyroidal uptake (Fig. 4).

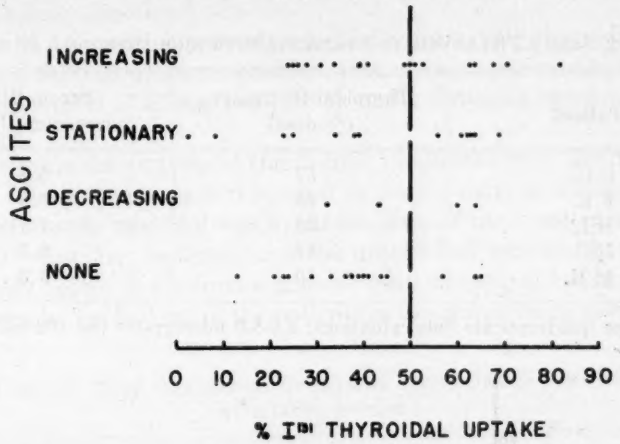

FIG. 4. The I^{131} thyroidal uptake in patients with and without ascites.

Categories of ascites illustrated here are based on changes that were observed to be taking place and not necessarily related to the amount of ascites present. Three patients with high I^{131} thyroidal uptakes had elevated blood urea nitrogen levels. There was 1 such patient in each of the groups with ascites. One patient with cardiac cirrhosis is included in the increasing group with a 31 per cent uptake; the other is in the group without ascites with 65 per cent uptake. Patients with hemochromatosis and infectious hepatitis had no ascites and 41 and 45 per cent thyroidal uptakes, respectively. All other patients in this chart had Laennec's cirrhosis.

In order to explore further the mechanism of high I^{131} thyroidal uptake in patients with diseases of the liver, serum protein-bound iodine (PBI) determinations were carried out in duplicate on 5 patients with thyroidal

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*=for basis of grading, see text.

Biopsies or postmortem examinations were performed within six weeks of the time of the radioiodine uptake, except in 1 patient marked (x) in whom the interval was six months.

One of the patients with liver damage graded II had an elevated level of blood urea nitrogen at the time the I^{131} thyroidal uptake was 57 per cent.

The patient with hemochromatosis had a 41 per cent thyroidal I^{131} uptake and cellular damage was classified Grade I. All other patients in this illustration had Laennec's cirrhosis.

uptakes of 50 per cent or more. It will be seen in Table 2 that the PBI level in all of these patients was normal.

Simultaneous multiple measurements of I^{131} thyroidal uptake and urinary excretion were performed on 8 patients. In the 3 patients who had a high 48-hour uptake, the accumulation of I^{131} was essentially complete in twenty-four hours. An example is seen in Figure 5. In these same patients

TABLE 2. SERUM PBI LEVELS IN 5 PATIENTS WITH HIGH THYROIDAL I^{131} UPTAKES

Patient	Thyroidal I^{131} uptake (% dose)	Serum PBI* (micrograms/100 ml.)
C.G.	57	5.9
F.K.	64	5.8
H.L.	63	7.1
H.C.	64	6.7
M.H.	50	6.6

* Average quadruplicate determinations; 4.0-8.0 micrograms per 100 ml. is normal range.

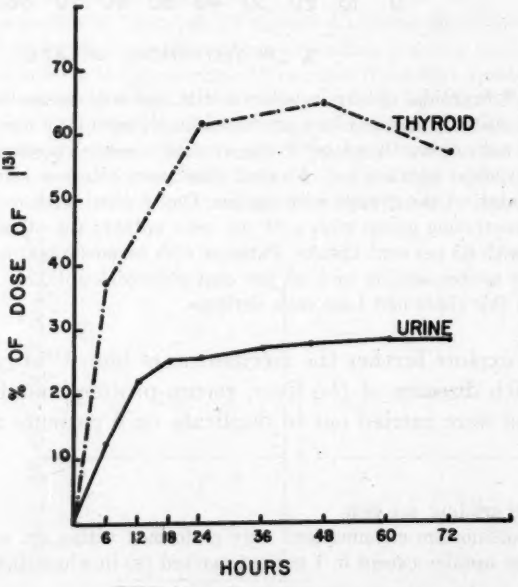

FIG. 5. The accumulation by the thyroid, and the urinary excretion of I^{131} in a patient with cirrhosis.

The renal excretion rate, calculated according to the method of Keating *et al.* (2), was 7.5 per cent per hour (normal range, 6.0–9.0). Thyroidal accumulation was 14.2 per cent per hour (normal range, 0.5–6.8). This sample patient had a marked degree of ascites.

with a high thyroidal uptake there was a normal urinary excretion curve. The renal excretion rates, as described by Keating *et al.* (2), were 7.5, 8.2, and 14.6 per cent per hour in these 3 patients. The rates of accumulation of I^{131} in the thyroid were 14.2, 12.3 and 22.2 per cent per hour, respectively. These observations indicate that renal excretion was normal and that the high thyroidal uptake in these sample patients was not caused by impaired kidney function.[5]

In 3 of the 5 remaining patients who had a normal I^{131} thyroidal uptake there was a delayed urinary excretion. One of these patients had a blood urea nitrogen level of 20 mg. per 100 ml. and 1 showed a trace of albumin in the urine.

To determine the activity of the thyroid in another way, the mean cell-height of the epithelium was measured in the thyroids of 5 patients from whom postmortem material was available. Two of the 5 patients had had elevated I^{131} uptakes; however, in 1 the uptake had returned to a normal level shortly before death from a massive gastrointestinal hemorrhage. As may be seen in Table 3, all of the patients in this group had a normal mean

TABLE 3. MEAN CELL-HEIGHT OF THYROID EPITHELIUM IN PATIENTS WITH LIVER DISEASE

Patient	Thyroidal I^{131} uptake (% dose)	Mean thyroidal cell-height (μ)	Weight of thyroid (Gm.)	Cause of death
Patients with liver disease				
K.G.	26	5.50	12	Liver failure
J.S.	50	5.58	29	Hemorrhage from esophageal varices
J.S.	13	5.61	—	Myocardial infarct
C.M.	69.4	6.46	19	Hemorrhage from esophageal varices
L.K.	23.7	6.54	22	Liver failure and cardiac failure
Control group				
F.G.	—	4.65	31	Cerebrovascular accident
C.F.	—	6.06	22	Cerebrovascular accident
M.B.	—	6.10	25	Cerebrovascular accident
L.W.	—	6.12	23	Cerebrovascular accident
S.L.	—	6.40	22	Cerebrovascular accident

[5] It should be pointed out that these 3 patients had moderate to serve ascites.

cell-height when compared to an equal number of patients who died of other causes without evidence of liver or thyroid disease.

In 12 patients, a second I^{131} thyroidal uptake test was made after an interval of from two to twenty-two months. At this time the clinical condition of the patients with Laennec's cirrhosis was noted. In those whose clinical condition had deteriorated, there was an increase in the I^{131} thyroidal uptake. Among those in whom clinical improvement had been noted, there was usually a decline in I^{131} uptake. After 1 patient with cardiac cirrhosis improved dramatically following mitral commissurotomy and 1 patient recovered from infectious hepatitis, significantly lower uptakes were observed (Table 4).

DISCUSSION

Since the I^{131} uptake by the thyroid was found to be elevated in 40 per cent of the patients in this series, the possibility of thyroid hyperactivity was suggested.

Kydd and Mann (5) in a study of 21 patients with cirrhosis found the

TABLE 4. COMPARISON OF THYROIDAL UPTAKES FOLLOWING FIRST AND SECOND DOSES OF I^{131} IN 12 PATIENTS WITH LIVER DISEASE

Patient	Original thyroidal I^{131} uptake (% dose)	Interval (months)	Clinical course	Subsequent thyroidal I^{131} uptake (% dose)	Remarks
J.K.	12	5	Worse	26	Repeated paracentesis required
N.S.	17	2	Worse	33	Increasing jaundice
G.A.	18	5	Improved	43	Spider angiomata disappeared
H.L.	60	22	Improved	63	Less ascites
A.R.	42	9	Improved	40	Jaundice disappeared
F.K.	82	3	Improved	64	Spider angiomata fading; ascites remained
V.S.	65	12	Improved	42	Cardiac cirrhosis; markedly improved by mitral commissurotomy
M.T.	63	11	Improved	35	Gross clinical improvement
S.H.	63	9	Unchanged	45	Jaundice and ascites remained
J.S.	50	8	Improved	24	Spider angiomata fading
E.K.	33	10	Improved	18	No need for paracentesis or diuretics for several months
W.S.	45	12	Recovery	25	Acute infectious hepatitis

serum protein-bound iodine concentration to range from 1.0 to 8.8 micrograms per 100 ml. In only 2 was the level above 7.8, the limit of normal. Indeed, low values were reported to be more common and were usually associated with a low level of serum albumin. In contrast to cirrhosis, the early phrase of hepatitis was commonly associated with PBI levels as high as those usually seen in thyrotoxicosis. The PBI level fell with time, but was not necessarily associated with recovery of liver function or subsidence of jaundice.

Barrelet (6) reported that basophilic granulation of the colloid of the thyroid occurred in 79 per cent of patients with cirrhosis and a decrease in the size of the thyroid occurred in 31 per cent. In the present study the increased production of thyroid hormone was not confirmed by clinical evidence or the results of BMR, PBI and cell-height determinations.

In view of these observations, it is probable that mechanisms other than those in the thyroid may be the primary cause of the high I^{131} uptake. The work of a number of authors indicates that the kidney is abnormal in some patients with cirrhosis. Adlersberg and Fox (7) observed that diuresis following a water test was delayed or diminished in patients in the late stages of cirrhosis with considerable hepatic damage. Baxter and Ashworth (8) found tubular degeneration of the kidneys in patients dying with cirrhosis but without known renal disease. Epstein *et al.* (9) showed that there was a very low urinary excretion of sodium in some patients with cirrhosis, that a profound salt retention could occur in the presence of a normal glomerular filtration rate and that sodium retention was due to excessive tubular reabsorption. Leslie *et al.* (10) observed that the filtration rate, effective renal plasma flow and maximal tubular excretion of *p*-aminohippurate were reduced during a period of ascites formation. It has been shown by Keating *et al.* (2), Skanse (1), and Perry and Hughes (11) that disease of the kidney may cause an abnormally high or low thyroidal uptake of I^{131}. The disappearance of I^{131} from the blood is prolonged and the thyroid may continue to accumulate I^{131} over a longer period than usual. This is manifested by a thyroidal uptake curve which does not level off in about twenty-four hours, as in normal subjects or patients with thyrotoxicosis, but continues to climb for a longer period. Furthermore, the failure of the kidneys to clear I^{131} promptly is shown by substantial amounts of I^{131} appearing in the urine after twenty-four to thirty-six hours. All of these observations point to the possibility that abnormal kidney function may be the cause of an abnormal I^{131} thyroidal uptake in patients with liver disease. Despite this evidence for renal abnormalities in patients with cirrhosis, in the 3 patients in whom a high I^{131} uptake was observed and in whom the renal excretion rate was studied, no evidence of an impaired rate of output by the kidney was demonstrable.

Kidney function may effect thyroid function in another way. Recant and Riggs (12) have shown that in nephrosis the serum protein-bound iodine level may be subnormal and the thyroidal accumulation of I^{131} accelerated. They found that when the synthesis of thyroid hormone was blocked by a goitrogen for a few days in these patients, the administration of thyroid-stimulating hormone would not raise the PBI level, as it does in a normal subject. It thus appeared that the thyroid was secreting its hormone but not storing it. Riggs has shown that PBI may be lost through the kidney with albumin. Such a mechanism seems very unlikely in the patients studied, because only a few of them had albuminuria. Moreover, the PBI levels and the mean-cell height of the thyroids were normal.

It is well established that some hormonal relationships may be altered by disease of the liver (13–15); an example is the failure of destruction of estrogens. In this respect, the unusual incidence of spider angiomata in the patients with a high thyroidal uptake of I^{131} was interesting. If the liver is an important route of excretion for endogenous thyroxine, as was suggested by Gross and Leblond (16), then a high PBI level and a decreased thyroidal I^{131} uptake might be expected when there is hepatic failure. If, however, most of the thyroxine secreted into the bile re-enters the blood in an enterohepatic circulation (17), the net effect of liver failure on thyroidal function may not be predictable.

Our observations give no strong clue to the mechanism of the high I^{131} thyroidal uptake in patients with liver disease. This study merely indicates that a high uptake does occur and may be misleading in patients whose symptoms might require the exclusion of thyrotoxicosis.

SUMMARY

The I^{131} thyroidal uptake was 50 per cent or higher in 20 out of 50 patients with liver disease but no evidence of thyroid disease.

Among the patients with liver disease, elevated I^{131} thyroidal uptakes were associated most frequently with spider angiomata, jaundice, and microscopic evidence of severe cellular damage of the liver.

No correlation could be established between elevated I^{131} thyroidal uptakes and either the presence of ascites or the results of any single test for liver function.

In spite of the elevated I^{131} uptakes by the thyroid in some patients with liver disease, there was no evidence for increased production of thyroid hormone, either by clinical findings or by laboratory determinations of the basal metabolic rate, the serum protein-bound iodine level or the height of thyroid cells.

Although abnormal kidney function may be present in patients with cirrhosis, the normal urinary excretion of radioiodine found in sample pa-

tients in this series indicated that renal disturbance at the time of the tests was not the cause of the elevated I^{131} thyroidal uptakes.

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QUANTITATIVE MEASUREMENTS OF RADIOIODINE RETENTION IN THYROID CARCINOMA*†

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DURING the course of radioiodine therapy, we have been interested in measuring the amount of radioiodine retention in functioning thyroid carcinomas for two main reasons: 1) to find how the degree of retention changes from dose to dose, and whether this measurement offers a criterion as to the progress of treatment, and 2) to determine the speed of radioiodine turnover in these tumors, since this is relevant to the amount of radiation delivered by each dose.

For both of these purposes, a rapid and robust method is needed for measuring the radioiodine content of the tumor or of its metastases daily after each dose, and under comparable conditions from year to year during treatment. Several procedures might be used for this purpose, and we have obtained serial measurements extending over two and a half years in a group of patients with functioning tumors by the following method:

METHOD

The patient lies on a couch over which a counter is moved horizontally, the counting rate being determined at points along the length of the body (1). The counter is so shielded as to respond to the radioiodine in the whole width of the body but in only a short section of its length opposite to the counter. In this way a "profile" curve may be drawn, indicating the isotope distribution along the length of the body; and peaks on this curve will correspond to sites of radioiodine concentration. The organs or positions with which these peaks correspond may then be identified by conventional mapping methods. The counting rate at peaks opposite to tumor deposits may be related to the percentage of the dose concentrated in the tumor tissue. If such profile measurements are repeated daily for one or two weeks after each dose, the radioiodine turnover of the tumor can then be determined; or if the counting rates opposite tumor deposits are compared after successive doses, using the same positioning of the patient and at equal

* Presented at the Annual Meeting of the American Goiter Association, Boston Mass., April 29–May 1, 1954.

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† Based on work undertaken for the Medical Research Council, London.

times after the dose, the changes in tumor uptake of radioiodine can be compared from dose to dose.

RESULTS AND DISCUSSION

Using this method we have measured the percentage of each dose that is found to be concentrated in the main or recognizable tumor sites (2). In patients with clearly functioning tumors, examined after thyroid ablation, the total tumor uptake commonly falls progressively from dose to dose; and the uptake of any one dose is usually between 30 and 80 per cent of that of the previous therapeutic dose (Figs. 1 and 2).

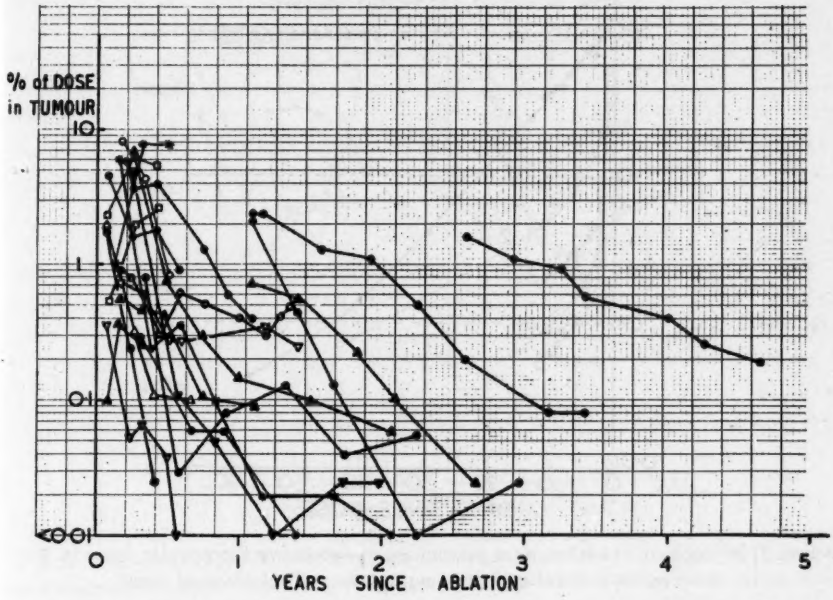

FIG. 1. Retention of successive therapeutic radioiodine doses by functioning thyroid carcinomas in 22 patients.

Ordinate. Total percentages estimated as present in tumor tissue at five days after each therapeutic dose (logarithmic scale).

Abscissa. Interval since thyroid ablation. For each patient points are plotted for all therapeutic doses given since profile measurements were started.

Now this is what would be expected if each dose achieved its intended purpose of destroying a certain fraction of the tumor tissue present in the body, the remainder retaining its powers of iodine concentration. On the other hand, the result might be ascribed to inhibition of uptake without reduction of tumor mass. Such inhibition of the uptake of any one dose by the irradiation caused by a previous dose certainly occurs if the time inter-

val between therapeutic doses is only a few weeks, but it is not probable when the intervals range from six to twenty-six weeks, as in our study. In many of these cases, moreover, such a possibility has been excluded by examining the completeness of recovery from the previous dose by means of tracer doses.

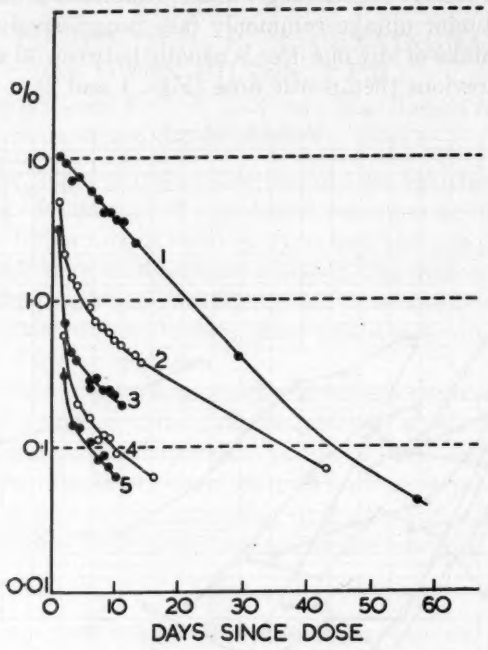

FIG. 2. I^{131} content of tumor, as a percentage of successive therapeutic doses in the same patient, showing decreasing uptake and retention of doses.

Alternatively, a progressive fall might be due to loss of tumor differentiation and function, and it is likely that this phenomenon sometimes occurs. In many of our cases, however, the fall was associated with loss of symptoms or with direct evidence of decreasing tumor mass, and it seems most unlikely that the reduction is ordinarily due to anaplastic changes in the tumor. The subject requires much further investigation; for example, by direct measurement of tumor iodine-concentrating efficiency by means of serial biopsy (3). Provisionally, a progressive fall in total tumor radioiodine uptake from doses at six-week intervals or more seems worth considering as an indication of a corresponding destruction of tumor tissue. It has been our aim to give doses of 100 to 150 millicuries at such intervals as to ensure such a progressive fall. For a tumor with active iodine concentration after

thyroid ablation we normally give these doses at intervals of from six to eight weeks, until the total tumor uptake falls below 1 per cent of the dose; then at intervals of from three to four months, until the uptake is less than 0.1 per cent; and then at intervals of from six to nine months, until uptake is of only 0.01 per cent or is no longer detectable.

The policy of repeating radioiodine doses, to aim at the destruction of a tumor rather than the arrest of its spread, is based on the view that more

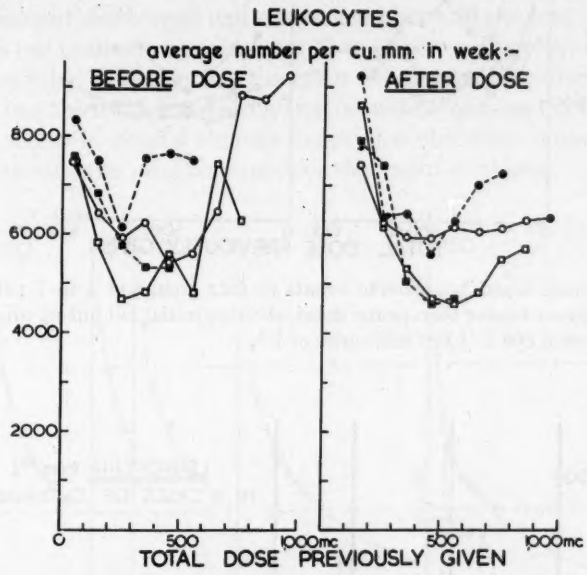

FIG. 3. Average blood leukocyte counts in four groups of 4 to 7 patients each, before and after successive therapeutic doses, showing initial fall but no progressive fall with total doses of 500 to 1,000 millicuries of I^{131}.

patients die from the effects of active tumor tissue than from radiation aplasia of the bone marrow during treatment. With repeated 150-mc. doses, the average numbers of blood leukocytes and lymphocytes fall to a moderate extent with the first few doses but usually do not fall further despite continued dosage, except for the transient decrease of these values which occurs during the two or three weeks following each dose.

Figures 3 and 4 give mean values in all 21 of our patients who received over 500 mc., arranged in 4 groups according to the total dose received. They show the values observed with increasing total dosage, as based on blood counts made either before, or in the week after, each therapeutic dose. Figure 5 gives values for the 4 patients in whom a lowering of blood

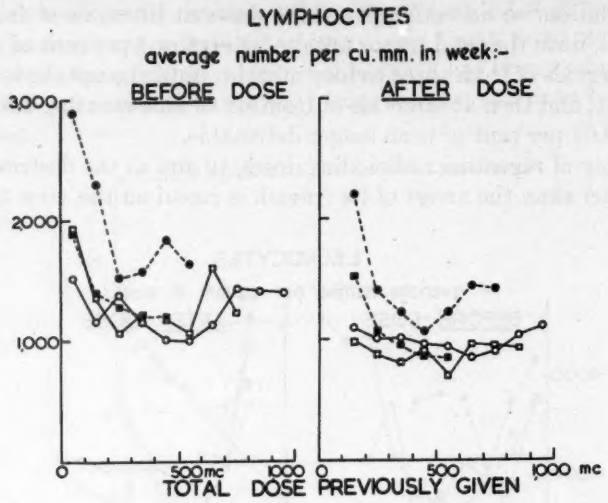

FIG. 4. Average blood lymphocyte counts in four groups of 4 to 7 patients each, before and after successive therapeutic doses, showing initial fall but no progressive fall with total doses of 500 to 1,000 millicuries of I^{131}.

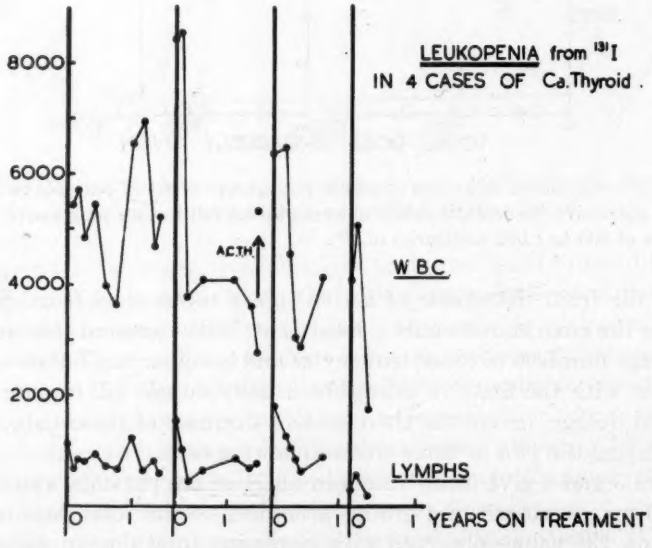

FIG. 5. Blood leukocyte and lymphocyte counts in 4 patients showing evidence of marrow depression. Plotted points give mean values for the week preceding successive test or therapeutic doses.

count, either in white cells, platelets, or red cells, was sufficient to delay treatment, and in 1 case probably to cause death. It does not appear that the risk of marrow aplasia is sufficient to exclude intensive treatment if this offers a prospect of the complete destruction of an iodine-concentrating tumor.

The rate at which radioiodine is discharged from tumor tissue may be examined by comparing profile measurements on successive days after a dose. The radioiodine turnover of tumor tissue is commonly rapid (1, 4, 5, 6). The amount discharged daily averaged about 20 per cent of the tumor content in our patients, varying from 10 to 40 per cent per day in individual cases. This rapid discharge has the effect of reducing the tumor irradiation to about one third the irradiation that would be obtained if the retention were as good as in normal thyroid tissue. It is obviously important, therefore, to examine the possible causes of this rapid discharge.

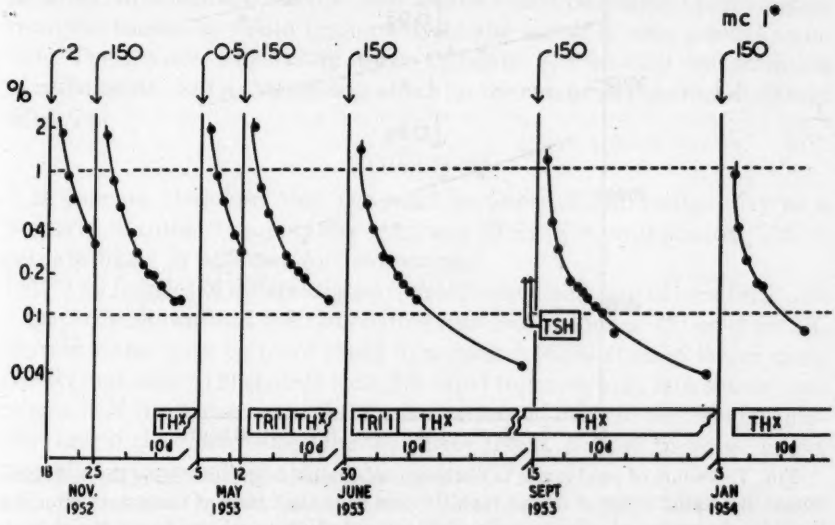

FIG. 6. Radioiodine content of a functioning thyroid carcinoma measured in the same patient as a percentage of successive I^{131} doses in the days following the doses, illustrating that the rapid discharge from the tumor is not influenced by

(a) size of dose—curves 1 and 2; 3 and 4.

(b) thyroxine therapy ("Thx," 0.4 mg. per day from forty-eight hours after the dose) —dose curves 2 and 7.

(c) triiodothyronine therapy ("Tri'I," 0.1 mg. per day from twenty-four hours after the dose)—curves 2, 4 and 5.

(d) continued thyroxine therapy throughout (0.8 mg. per day), with injection of thyroid-stimulating hormone ("TSH," 10 mg. Armour at thirty-six and at twelve hours before the dose). There is a slight fall in tumor uptake at comparable intervals after successive therapy doses.

In the first place it might be due simply to the effects of tumor irradiation by the radioiodine, or possibly to the carrier content of the therapeutic doses (which may exceptionally reach 0.75 mg. of iodine) for it is certainly true that the discharge of a therapeutic dose may be more rapid than that of a preceding test dose. In other cases, however, both such doses may be equally and very rapidly discharged, so that this appears to be an improbable explanation (Fig. 6).

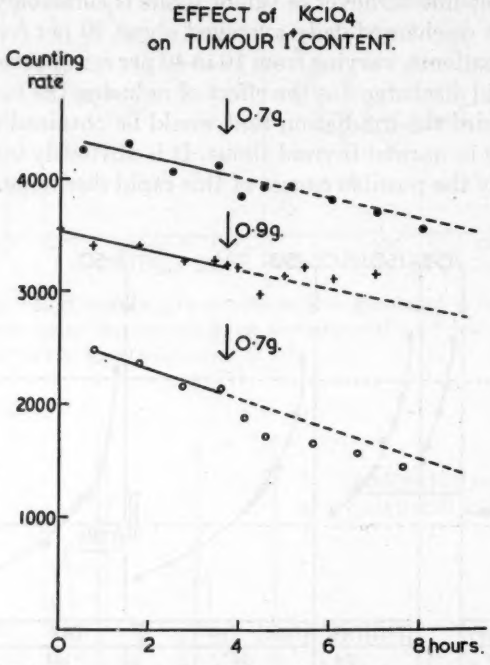

FIG. 7. Failure of perchlorate to discharge radioiodine from functioning thyroid carcinomas in 3 patients tested during rapid I^{131} loss from the tumor at three days after the dose; full depression of salivary radioiodide concentration was shown to occur with each of these doses. (Size of oral doses in grams.)

Alternatively, this rapid turnover might be ascribed to intense stimulation by thyroid-stimulating hormone (TSH), since the tumor metabolism is normally studied after thyroid ablation in a myxedematous patient who has discontinued thyroxine treatment for four weeks before the dose. This explanation is improbable, since a rapid turnover may be observed before the onset of myxedema; also it has been found that treatment designed to decrease TSH release from the pituitary does not influence the rate of turnover. Thus, .

1. If thyroxine treatment is re-started twenty-four hours after the dose,

when the tumor uptake of radioiodine is complete, the rate of discharge is not reduced in the ensuing week (Fig. 6).

2. The same is true if triiodothyronine is given at this time in the hope of inducing a more rapid inhibition of the pituitary than is obtainable by thyroxine.

3. The discharge rate is also uninfluenced if an attempt is made to suppress endogenous TSH entirely by maintaining the patient on thyroxine before and after the radioiodine dose, stimulating uptake by the injection of TSH before the dose only.

A further possibility is that the rapid turnover occurs because part of the tumor radioiodine is present in the form of iodide, an increased tumor iodide space resulting either from a long-continued action of TSH or from peculiarities in tumor metabolism. To test this hypothesis, potassium perchlorate was given to 3 patients at a time when the rapid discharge was in progress, to determine whether radioiodine would be emptied immediately from the tumor, as would presumably be the case if it were present as iodide. These doses, which were shown to inhibit the salivary concentration of radioiodide, had no significant effect on the tumor radioiodine discharge (Fig. 7).

CONCLUSIONS

It appears, therefore, that the rapid turnover of radioiodine may be a property of tumor tissue, rather than any effect of its stimulation. This is perhaps likely in any case for two reasons:

1. The follicles of differentiated thyroid carcinomas are of small size and it has been shown that the radioiodine turnover of human (7) or of rat (8) thyroid tissue may be more rapid in smaller follicles than in larger ones. Nadler and others (8) showed that this rapid turnover may be a simple consequence of the higher ratio of cell mass to colloid mass in the smaller follicles; and if the same holds true for tumor tissue, a rapid turnover might possibly be expected for this reason alone.

2. In normal thyroid tissue, radioiodine passes rapidly from the cells to the colloid so that, in effect, the cells are the medium for uptake and the follicles for retention of radioiodine. For these reasons, tumors consisting mainly of functioning cells which are not arranged in follicles might take up radioiodine but discharge it as rapidly as has been shown to occur.

For either of these reasons a poor retention of radioiodine in many thyroid carcinomas might be a consequence of the paucity or smallness of their follicles.

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OF THE ORIGIN, CHARACTERISTICS AND BEHAVIOR OF THYROID CANCER*

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HISTORICALLY, positive identification of thyroid cancer has been characterized by a struggle with the pleomorphism of the tumors. Malignant neoplasms of the thyroid can resemble benign neoplasms or even normal thyroid architecture so closely that for many years the "benign" metastasizing goiter of Cohnheim (1876) (1) was believed to be a definite entity. This appeared to defy the laws of biologic behavior of malignant neoplasms. A modification of this concept occurred when Langhans in 1907 (2) described the condition as "proliferating goiter," thus at least side-stepping a contradiction in terms. The confusion has been perpetuated by the relative infrequency of occurrence of thyroid cancer and by the long natural history of the less malignant phase of the disease. These two factors have contrived to limit observations on a sufficiently large number of patients over a period of time long enough to relate any of the histologic patterns (except the Group III cancers) with predictable behavior and prognosis. Even in the Group III cancers there are surprising exceptions.

This confusion is reflected also in the many and varied classifications which have been proposed, even though the tendency has been toward simplification (3, 4, 5). It has been established that there are two principal forms of the less malignant tumors, namely, papillary and follicular. There are many variants of these and it is realized now that the pleomorphism may exist not only in the primary tumor but in the metastases.

Group I tumors are characterized in general by their relatively benign nature and Group III tumors by their very malignant nature. The Group II tumors lie in between and ultimately fall into either Group I or III, depending upon behavior. Recently many malignant goiters have been described which, although predominantly papillary or follicular (or variants of these), have been found to consist of mixtures of both. The histologic appearances of the metastases have been found to vary also. Usually, but

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not always, they follow the predominant pattern of the primary tumor. This form of Group I neoplasm is called "mixed" thyroid carcinoma.

In general, clinical reports of methods of treatment, prognosis and outcome have been made with reference to the morphologic types of neoplasms alone, based upon the classifications which have been adopted by the observers making the reports. Most of these state the results of five or ten year follow-up observations on small groups. It can be shown, however, in a significantly large group of patients that these malignant neoplasms may exist unrecognized, due to mistakes in the original histologic diagnosis, for well over ten years. Estimates of degrees of malignancy based upon statistical data from such reports must be examined critically and accepted with caution. The reasons for this attitude, and the importance of understanding the behavior of these neoplasms should become apparent in the discussion which follows. The principal areas of contradiction and dispute are concerned with the origin, characteristics and behavior of thyroid cancer. The following discussion is based chiefly upon a careful study of thyroid cancer and nodular goiter over the past thirty years at the Presbyterian Hospital in New York City.

I. ORIGIN

The origin of thyroid cancer in the broad sense is as much an enigma as that of any other neoplasm. The association of hyperplasia and neoplasia is cited as of such frequent occurrence that there is thought to be more than a casual relationship between the two (6). Thyroid cancer is thought generally to develop within adenomatous glands. The assumption is that at some time within the life span of these goiters there occurs a change from benignancy to malignancy, with corresponding alterations in morphology and behavior. Certainly it is true that the distinctions between malignant and nonmalignant neoplasms are often so slight histologically that the benign origin of thyroid cancer is plausible. This is generally assumed to be the origin of most thyroid cancers.

The presence of blood vessel invasion is strong evidence of malignant change as established by Graham in 1924 (7) and re-affirmed by observations since then (8). It is one of the most dependable criteria in the diagnosis of thyroid cancer. It is no guide to prognosis, however, nor to the degree of malignancy in any given tumor.

Associated Pathologic Changes

Careful studies of nodular goiter and thyroid cancer carried out during the past several years at the Presbyterian Hospital in New York City have shown that cancer of the thyroid is found in association with every type of

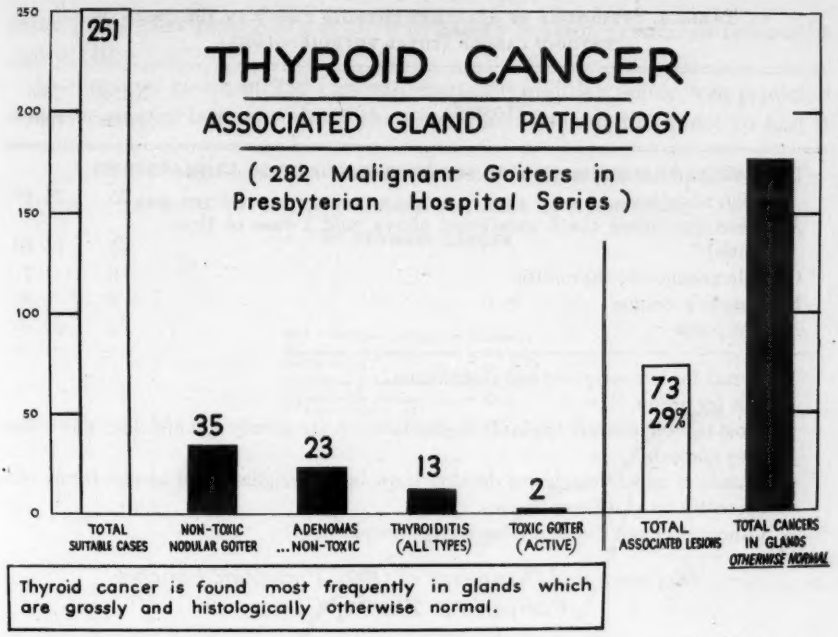

FIGURE 1

goiter. The actual incidence of other pathologic changes in the gland is difficult to assess, because ordinarily only a portion of the gland is examined.

In Figure 1, the associated changes reported by the Surgical Fathology Department at the Presbyterian Hospital in 282 thyroid cancers are summarized. In Table 1, a much more nearly complete and accurate appraisal of these findings is presented on a smaller group of cases. This recent study was made on 106 total thyroidectomies for cancer. The entire gland in each instance was carefully studied grossly and microscopically for other pathologic changes besides cancer.

Essentially the same conclusions were reached in both studies. Most of the thyroid cancers in these groups occurred in glands which otherwise were grossly and histologically normal. Clinical acknowledgment of this fact was attested by the high incidence of the "solitary nodule." The association of adenomas (true benign neoplasms) with cancer was high, and this seemed true likewise for nonspecific thyroiditis. The association of nontoxic nodular goiter on the other hand was about normal for age and sex distribution.

TABLE 1. STRUCTURE OF ADJACENT THYROID TISSUE IN 106 CASES OF THYROID CANCER (TOTAL THYROIDECTOMY)

Thyroid	No. of cases	Per cent
Nontoxic nodular goiter (5 of these also showed adenoma—true benign neoplasm)	25	24.0*
Adenoma (including the 5 mentioned above, and 1 case of thyroiditis)	16	15.0†
Chronic nonspecific thyroiditis	5	4.7
Hashimoto's struma	2	1.9
Normal gland	*64*	*60.0*

* Normal for sex ratio and age distribution.

† High for group.

1. Most thyroid cancers originate in glands which are grossly and histologically otherwise normal.
2. Glands in which neoplasms develop show both malignant and benign forms concurrently or at different times.
3. Cancer does not develop from benign neoplasm (?)

Incidence and Occurrence of Other Pathologic Changes Compared to Those of Cancer

1. *Simple nodular goiter*

It appears, therefore, that although cancer of the thyroid occurs in association with other pathologic changes in the gland, these other changes may simply exist there in the proportions of their natural incidence. This is not easy to establish, because the actual incidence of some of these other changes is not known.

Data are available, however, on the incidence of nodular goiter at various age periods in this country in an endemic region (9), in a nonendemic area (Boston) (10) and in Switzerland (11). These studies indicate that nonmalignant nodules are rare before puberty and that after this time they increase throughout the life span and are most commonly found both in endemic and sporadic areas after the age of 50, particularly in women. Cancer, on the other hand, as shown in the material studied at the Presbyterian Hospital and in that from other clinics, occurs in children before puberty and constitutes by far the most frequent pathologic change in nodular goiter at that age level (12). The peak of occurrence of nonmalignant nodular goiter in our hospital population is in the group between 40 and 50 years of age. If cancer developed from nodular goiter we should expect it to increase during the later years of life, *i.e.*, during "the cancer age" when simple nodular goiter is most common; but this is not the case (Fig. 2). Actually, recognizing the long natural course of the disease, it is much

more likely that most cases of thyroid cancer develop around or before the age of 40.

In our own group of 282 cancers, nontoxic nodular goiter was reported as an associated lesion in about the proportion one would expect to find it

DISCREPANCIES BETWEEN THE INCIDENCE OF SIMPLE NODULAR GOITER AND THE ESTIMATED INCIDENCE AND AGES OF OCCURRENCE OF THYROID CANCER

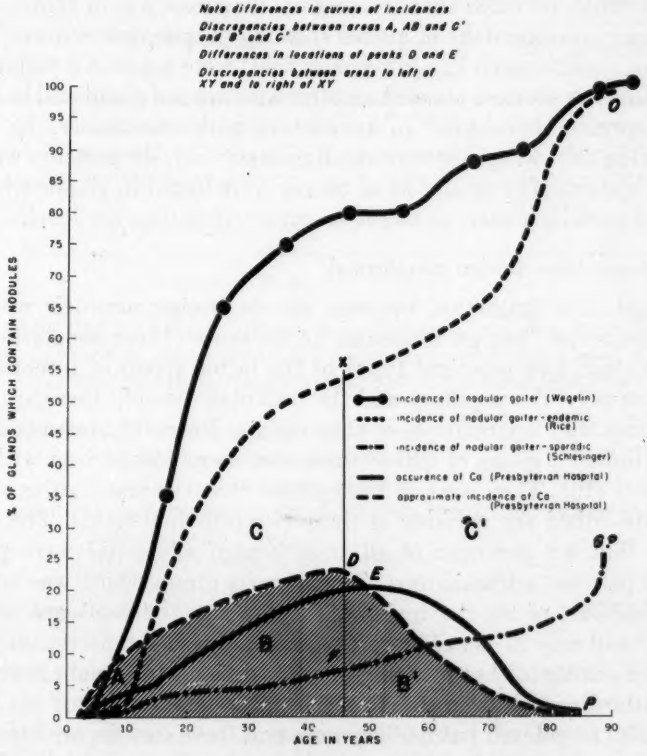
Note differences in curves of incidences
Discrepancies between areas A, AB and C' and B' and C'
Differences in locations of peaks D and E
Discrepancies between areas to left of XY and to right of XY
% OF GLANDS WHICH CONTAIN NODULES
AGE IN YEARS
incidence of nodular goiter (Wegelin)
incidence of nodular goiter - endemic (Rice)
incidence of nodular goiter - sporadic (Schlesinger)
occurence of Ca (Presbyterian Hospital)
approximate incidence of Ca (Presbyterian Hospital)
A
B
B'
C
C'
D
E
O
P

FIGURE 2

alone, according to age groups. Thus it was not reported by the Department of Surgical Pathology in any case under 25 years of age, although there were 39 cancers in this group. From that age on, it was reported with increasing frequency until the old age group was reached, in which the proportion of Grade III cancers was highest. These cancers tend to overgrow

and obliterate the other histologic features, so that any normal pattern or benign changes may not be noted. Undoubtedly re-examination of the material would now reveal more nontoxic nodular goiter than was reported and serial sections would reveal even more. Nevertheless, the highest incidence of nontoxic nodular goiter was reported by the pathologists to be within the age group in which its presence was most obvious, that is between 41 and 50. Even here, only 15 cases were reported in a group of 66 cancers.

Furthermore, in a small group of patients with known cancer, re-examination of the original sections years after the diagnosis of benign disease had been made, revealed that the original diagnosis was in error.

Histologic examinations of glands showing microscopic cancers (the entire tumor could be seen in a low-power field) were made in 2 young males. In one, multiple sections showed an otherwise normal gland and in the other, "nonspecific thyroiditis" in association with the cancer. In 4 other cases having microscopic or very small primary foci, the patients were middle-aged women. The small foci of cancer were found in glands which also contained nodular goiter, as might be expected at that age level.

2. *Adenomas (true benign neoplasms)*

Although the distinction between simple benign nontoxic nodules of nodular goiter and benign adenomas (in the sense of true neoplasms) is not sharp or clear, two principal types of the latter group of tumors are described, namely, the papillary and the follicular. Usually these are solitary but at times they are multiple or even diffuse. Recently Meissner and McManus studied a group of 500 of these tumors in comparison with malignant goiter (13). They were of the opinion that the many subgroups previously described are variants of these two principal forms. Their figures indicate that 4.8 per cent of all their benign adenomas were papillary and 86.6 per cent adenomatous. (There was a group which was not classified.) However, of all the malignant neoplasms, only 50 per cent were papillary and only 27 per cent were adenomatous. This discrepancy, which is roughly similar to that in our findings, is difficult to explain if we assume that cancer develops from simple benign adenomas.

Actually, as pointed out earlier, more and more cancers are being found to contain elements of both principal forms (papillary and follicular), *i.e.*, "mixed" cancer. The presence of papillary elements in an "adenoma" of the thyroid at once arouses suspicion that it may be cancer. The age of the patient at the historical onset of these adenomas tends to correspond more closely to that observed for cancer than for nontoxic nodular goiter.

3. *Cancer in recurrent nodular goiter (originally nonmalignant)*

In a group of 513 patients, following removal of goiters which histologic

examination proved to be nonmalignant, only 2 cancers have been found so far among 63 recurrences (Table 2). One might say that this proves the prophylactic value of partial thyroidectomy in nontoxic nodular goiter. However, the study has shown that the incidence of recurrence of nontoxic nodular goiter was over 25 per cent, and in many cases a portion of only one lobe was removed. As a matter of fact, in the 2 cases mentioned, the

TABLE 2. THYROID CANCER. FOLLOW-UP STUDY OF 513 THYROID TUMORS OPERATED UPON AS NONMALIGNANT NODULAR GOITERS

No. of cases	Histologic diagnosis	Re-operation		Cancer found	
		No. of cases	Per cent	No. of cases	Per cent
371	Nontoxic nodular goiter	41*	11	0	0
82	Adenoma	8†	10	2	25
24	Nontoxic diffuse goiter	4	17	0	0
22	"Toxic"	9	41	0	0
14	Chronic nonspecific thyroiditis	1	7	0	0
513		*63*	*13*	*2*	*3*

* An additional 43 patients, with similar indications, refused re-operation.

† There has been no recurrence of the original type of benign tumor, even though nontoxic goiter subsequently developed in that part of the gland from which the tumor was removed.

Length of follow-up: 5 years or longer—354 cases
10 years or longer—259 cases
15 years or longer—149 cases

Recurrences: (45 questionable—under observation, but without definite indication for re-operation)
Total possible—129, or 34 per cent
No recurrence—242, or 66 per cent.

Cancer—so far, found only in Adenoma group.

cancers were found in tissue which was described as "normal" by the surgeon at the time of the initial procedure. This tends to confirm the earlier statement that cancer develops in "normal" gland. In these 2 cases the tissue which was removed and examined initially was found to contain true adenomas. This experience with regard to the discovery of cancer in recurrent simple goiter is illustrated in Figure 3.

Sex Ratios in Thyroid Cancer

It is believed generally that the incidence of thyroid cancer in women is between two and three times the incidence in men. This deserves more critical analysis and further breakdown; obviously the sex factor is im-

portant, since goiter itself is so much more frequent in women than in men.

In the group of cancer cases here reported the over-all sex distribution was as follows:

Females, 228—80 per cent
Males, 54—20 per cent
} a ratio of 4 to 1

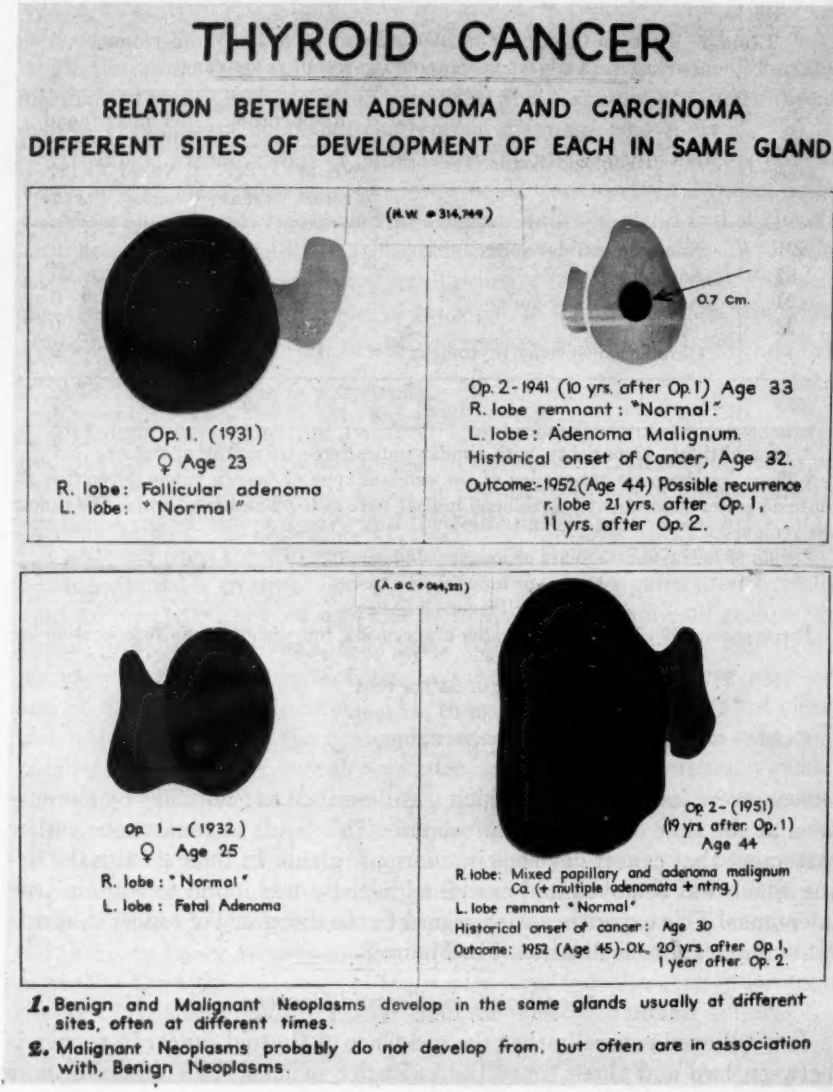
THYROID CANCER
RELATION BETWEEN ADENOMA AND CARCINOMA
DIFFERENT SITES OF DEVELOPMENT OF EACH IN SAME GLAND
(M.W. # 314,749)
Op. 1. (1931)
♀ Age 23
R. lobe: Follicular adenoma
L. lobe: "Normal"
0.7 Cm.
Op. 2 - 1941 (10 yrs. after Op. 1) Age 33
R. lobe remnant: "Normal"
L. lobe: Adenoma Malignum
Historical onset of Cancer, Age 32.
Outcome:-1952 (Age 44) Possible recurrence
r. lobe 21 yrs. after Op. 1,
11 yrs. after Op. 2.
(A.o.c. # 064,221)
Op. 1 - (1932)
♀ Age 25
R. lobe: "Normal"
L. lobe: Fetal Adenoma
Op. 2 - (1951)
(19 yrs. after Op. 1)
Age 44
R. lobe: Mixed papillary and adenoma malignum
Ca. (+ multiple adenomata + ntng.)
L. lobe remnant "Normal"
Historical onset of cancer: Age 30
Outcome: 1952 (Age 45)-O.K. 20 yrs. after Op. 1,
1 year after Op. 2.
1. Benign and Malignant Neoplasms develop in the same glands usually at different sites, often at different times.
2. Malignant Neoplasms probably do not develop from, but often are in association with, Benign Neoplasms.

FIGURE 3

In a nationwide survey of thyroid cancer in children (0–15 years of age), Winship (12) in 1951 reported 66.6 per cent females among a total of 189 patients. This is a ratio of 2 females to 1 male in children. In the elderly, the ratio was found to be 3:1 in our series. In the group between 26 and 40 years of age in our series the ratio was 8:1. In these studies it is interesting that at the opposite ends of the life span the sex ratios in thyroid cancer approached each other, whereas in the middle-age groups the cancers occurred preponderantly in women.

Experimentally Produced Cancer

The experimental production of thyroid cancer, or of other cancer for that matter, does not presuppose the existence of histologically abnormal tissue within the organ. The investigator usually starts on the assumption that the tissues are normal. In such glands, experimentally induced thyroid cancer capable of metastasizing has been produced by the administration of goitrogenic agents to animals (14, 15, 16). These drugs have produced hyperplasia in the glands of experimental animals, although obviously neoplasia has developed in what originally was normal gland histologically. The same is true of tissues in which cancer develops during treatment with other carcinogenic substances or agents such as radium, x-ray and other forms of radiation (17). This is not to say that abnormal tissue such as adenomas within the thyroid gland may not, or do not, respond in a similar manner. The point is that there is much evidence to support the contention that most thyroid cancer probably develops from gland which is histologically normal. At any rate, the most that can be said with any assurance is that, of all nodular glands, cancers are more likely to develop in those which contain true adenomas than in those that do not contain true adenomas; but that the adenomas which develop do not themselves necessarily change into cancers. It has been observed also that in glands which contain cancer, occasionally benign adenomas develop subsequently in remnants left behind at the time the cancer was removed.

To repeat, cancers develop most frequently in glands which otherwise appear histologically normal, frequently in glands which also contain benign adenomas, less frequently in glands showing nonspecific thyroiditis, and occasionally in association with nontoxic nodular goiter. Cancer is found least of all in association with active thyrotoxicosis (0.7 per cent).

One of the important implications of these observations is that any palpable nodule in the thyroid gland—indeed any nodule or mass visible under the microscope—which later proves to be a cancer, was probably a cancer from the time it began to develop. This does not mean it began at or near birth, although in young individuals this probably does occur. We can be quite certain that no age group is immune to cancer.

One of the most important practical clinical implications is that the

great significance of the solitary, discrete nodule applies particularly to those age groups in which nodules are uncommon, that is in children and juveniles. On physical examination, "solitary nodules" in middle-aged women usually turn out to be prominent nodules within nontoxic nodular goiters, which are common at that age. In young persons, however, nodular goiters, whether "solitary" or multiple, must be regarded very seriously as possible cancer (Fig. 2).

II. CHARACTERISTICS AND BEHAVIOR OF THYROID CANCER

Most clinical reports dealing with thyroid cancer have been made with reference to the histologic groups defined by pathologists. Concepts of the characteristics of malignant goiter have been tied very closely to these histologic types. This has not been satisfactory, because results of treatment, prognosis and outcome have been found to show great variation within groups of tumors showing similar histologic patterns.

1. *Long natural history*

The clinical characteristics of thyroid cancer give us a somewhat different point of view. The most outstanding and obvious of these is the long natural course of the disease. Certain forms, notably the Hürthle-cell variety, seem to have an extremely long natural existence as relatively benign malignant neoplasms. Actually the Hürthle-cell cancer differs little in this respect from the other forms within this group. Apparent exceptions to this characteristically long life-span are the Group II and Group III cancers. These usually run a rapid and fatal course. It is the occasional exception to this behavior which is interesting. For this and other reasons which will be discussed, one is entitled to assume an attitude of skepticism toward accepting the thesis that they are fundamentally different neoplasms.

Of 7 patients up to 40 years of age in whom the disease was estimated to have existed for twelve years or longer at the time the diagnosis of cancer was established, it was estimated that the total duration of the disease (to the time of death in 3 patients, and up to the year 1951 in 4 living patients) was fourteen to thirty-seven years (in 6, it was twenty-two to thirty-seven years). In 43 patients aged 47 to 76 years, the total duration of the disease was twelve to fifty-two years. The great majority of all patients who had the disease for very long periods of time were 47 years of age or over when the diagnosis was established. Of the 43 patients between 47 and 76 years of age, 33 are now dead and the remaining 10 are living with disease (1951). It is apparent that patients can live with the disease for extremely long periods of time. This is well known, but it is interesting and not so readily apparent that in the older patients, who had the disease the longest, frequently the diagnosis was not made until late, and in these the mortality

rate was very high. This was true, regardless of the fact that the histologic types were the same as in the younger age groups in whom the disease had not lasted so long nor had the mortality rate been anywhere near so high. Yet in those few patients in the younger age group who had had the disease for a long period of time, the morbidity and mortality rates were very high also. Degree of malignancy, therefore, seems related to duration of the disease. Usually the older the patient, the older the disease and the greater the morbidity and mortality. Duration of the disease in itself, however, seems important in this respect, regardless of the age of the patient (Figs. 2 and 4).

Inadequacy of ten-year follow-up: In a disease having as long a "benign" natural course as thyroid cancer, it becomes obvious that a ten-year follow-up evaluation alone has little, if any, meaning. For example, in a group of 88 patients in whom there was history of a goiter for ten years or longer (a goiter which later was proved to be cancer) all were living at the time the diagnosis was established. Sixteen of these patients were found to have cancer at that time, *i.e.*, ten years after the historical onset of the goiter. Only 5 of these were found to have demonstrable metastases and only 1 had symptoms due to the cancer. However, 27 of this group were dead of thyroid cancer thirteen to fifty-two years after the estimated onset of the disease. A ten-year follow-up assessment based upon historical onset of the disease would have shown no mortality, whereas the ultimate mortality rate was 26 per cent in this same group (1951).

2. *Discrepancy between histologic evidence for diagnosis of cancer and prognosis*

One of the curious paradoxical characteristics of thyroid cancer is that, although the diagnosis may be correctly and accurately made using the histologic evidence of blood vessel invasion, lymphatic invasion, capsular invasion and invasion of normal adjacent gland as criteria, yet in no way are these findings to be relied on as guides to the degree of malignancy or to prognosis. A tumor with definite blood vessel invasion and actual invasion of adjacent structures usually is regarded as highly malignant. Such is not necessarily the case in thyroid cancer. These criteria were used in the diagnosis of all the cases in the series at the Presbyterian Hospital and yet it is obvious that not all the tumors behaved like malignant neoplasms. In many doubtful cases, time has shown that the criteria of diagnosis are valid; nevertheless, a large group of these patients lived with their disease for many years after both blood vessel and capsular invasion were demonstrated. Almost all of the younger patients in this group whose tumors were so diagnosed, even those in whom there was histologic evidence of actual invasion of adjacent structures, are still alive—and in some cases, after

barely minimal attempts to eradicate the disease. Studies of the patients who died reveal that most of them had the disease for long periods of time before the beginning of the terminal phase, and that the latter was much shorter than the "benign" phase. The mere fact of blood vessel, lymphatic, or capsular invasion, or even invasion of adjacent structures, could not be correlated with the incidence of distant metastases, with rapid downhill progression of the disease, nor with the prognosis in any other respect. (In the age group from 4 to 46 years, there were only 4 certain and 2 doubtful cases with distant metastases out of 135 patients (6/135). In the age group from 47 to 82 years, however, in patients with histologically similar tumors, there were 32 certain and 8 doubtful cases with distant metastases among 147 patients (40/147). Yet the criteria for the diagnosis of malignancy were the same in both groups.)

3. *Histologic types of thyroid cancer at various age levels*

Table 3 shows the occurrence of various histologic types of cancer, according to age groups.

Attention has been drawn to the fact that many of the Group I cancers have been found to be mixed forms rather than pure forms of papillary or follicular tumors. All of them have much in common from the standpoints of behavior and duration. Their chief differences appear to be in the manner and sites of spread, depending upon the predominant pattern in the primary tumor (?).

Table 3 shows the occurrence of Group I cancer at all age levels. There are fewer of these cancers in the first two decades than later. (The actual age of historical onset of thyroid cancer would show more cases in the first two decades than shown here.) The occurrence of Group I cancer diminishes after the age of 40 *at the same time that the occurrence of Groups II and*

TABLE 3. OCCURRENCE OF VARIOUS HISTOLOGIC TYPES OF CANCER, ACCORDING TO AGE GROUPS

Age of patient (yrs.)	Group I				Group II	Group III	? Type	Mod. undiff.	Total
	Pap.	Foll.	Hürthle	Mixed					
0–25	11	12		15	1?				39
26–40	30	12	1	20	4		1		68
41–50	18	23	2	12	5	4	1	1	66
51–60	10	14	7	4	5	8			48
61+	18	10	3	3	8	19			61
Totals	87	71	13	54	23	31	2	1	
			225			*54*		*3*	282

III increases. The total of all types of cancer, however, varies only slightly from one age group to another, except at the extremes of life, as discussed under the origin of cancer. It should be observed that in the present series of cases, before the age of 40, there were only 4 (plus 1 questionable) Group II cancers and no Group III cancers, whereas after 40 there were 18 Group II and 31 Group III cancers—which is about the usual reported distribution. Adding the latter to the Group I cancers tends to equalize the number of cancers found in the various age groups.

As pointed out, there is no essential difference histologically between a papillary, follicular, Hürthle-cell or mixed tumor at age 15 and at age 65. The same criteria for diagnosis are used at all ages and the microscopic appearance of the tumors is similar, even though there may be variations between individual tumors at any age. However, as we shall see later, there are very marked differences in behavior between youthful tumors and old tumors. The striking difference histologically between the tumors found in youth and in old age is the paucity of Group II and Group III cancers in youth and the relative frequency of these in the older age groups. Group III tumors frequently are entirely different morphologically from those in Groups I and II. It has been natural to assume, therefore, that they are different tumors altogether. Interestingly, the anaplastic tumors among the Group III cancers are occasionally found to contain elements which are similar to those in Group I. This has been interpreted as capacity for the tumor to differentiate into these forms. Another interpretation, apparently not considered heretofore, is the possibility that the tumor may have belonged to Group I originally and evolved into the Group III type. The fact that almost all of these tumors occur in older patients and that a significant number of them give a history of a truly pre-existing goiter which suddenly began to grow at an alarming rate, also suggests this sequence of events. In this connection, it is pertinent that the long-lived Group I cancers, often with little or no change in size at the primary site, are nevertheless capable of wide, distant and destructive spread with increasing age, without morphologic change.

4. *Variability in type and extent of thyroid cancer in the body*

Even though the histologic patterns of the various Group I cancers are similar at every age, it has been pointed out by many observers that there are clinical forms of the disease which appear to be characteristic of certain age groups. In young persons with thyroid cancer, for example, the disease is frequently more extensive in the neck, than in older subjects. Most of the patients who have been said to have "lateral aberrant thyroid" (18) gland tissue are in this group, and they constitute a sizable proportion of those between the ages of 4 and 30 in our series. To delineate this group is

somewhat difficult because, although often there is extensive cervical cancer, there is found to be involvement also of tissues in the lower neck around the trachea and esophagus, and in the mediastinum. Though the spread may be quite extensive it may not be apparent, except at operation or after histologic examination of tissues removed from these regions. Not infrequently, the disease is found microscopically in small, soft nodes, grossly entirely unsuspected of involvement. It is for this reason that one feels uncertain about the complete removal of the disease in this younger group of patients, even when a total thyroidectomy with conventional neck dissection has been performed. Knowing the many years these patients can live with their disease even when it is known that cancer is present, it must not not be assumed that just because a "radical" operation has been carried out, the patient is therefore free of disease. In the series here reported, the apparently excellent results of treatment in this age group with extensive disease contrasts with the extremely poor results of treatment in older age groups with identical histologic tumors and equally radical treatment combined not infrequently with the use of radioactive iodine. The relationship between age and mortality is represented in Figure 4, which also depicts the long duration of the process. This characteristic of the behavior of thyroid cancer has been discussed in recent papers by Crile (19) and Shofner (20).

In those patients having extensive local and regional lymphatic spread, no predominant type of cancer was found. The usual assumption has been that this clinical form of the disease represents strictly papillary cancer. In our experience this has not been true. The distribution has been roughly equal between the papillary, follicular and mixed types in patients before the age of 40 who have shown extensive cervical involvement.[1] Most of the Group I cancers actually are a mixed type, as previously stated. Why extensive local and regional spread of this cancer in such a benign form should occur so frequently in young patients is not understood. It has been pointed out also that the primary tumor may be microscopic or small and show little tendency to grow, or to recur if incompletely removed, even though the metastatic distribution is widespread. To the author, this seems to be a characteristic of the almost pure follicular type of cancer also. The rapid and wild overgrowth at the primary site is rather a characteristic of old cancer.

The Group I cancers we are discussing were further characterized in our series by the fact that more of them showed multiple foci within the gland than in older age groups. In the group of patients from 4 to 25 years of age, 12 of the 39 (almost one third) showed multiple areas within the gland.

[1] The youngest, aged 4, had a mixed follicular and papillary cancer with bilateral cervical node involvement. The oldest, aged 82, had a papillary cancer. Both, incidentally, are alive.

Since this is the group which is associated with such widespread local and regional cervical lymphatic distribution, the presence of multiple foci itself suggests, as Cope has held, that these may simply represent lymphatic distribution within the gland. The possibility of multicentric origins is recognized, however. In the age group 26–40, there were only 7 glands out of 68 which showed multiple foci; in the age group 41–50, 5 glands out of 66; in the age group 51–60, 5 glands out of 48; and in the age group 61 and over, possibly 1 gland out of 61, although within this group occurred the largest number of Group III tumors. As to the type of tumor showing

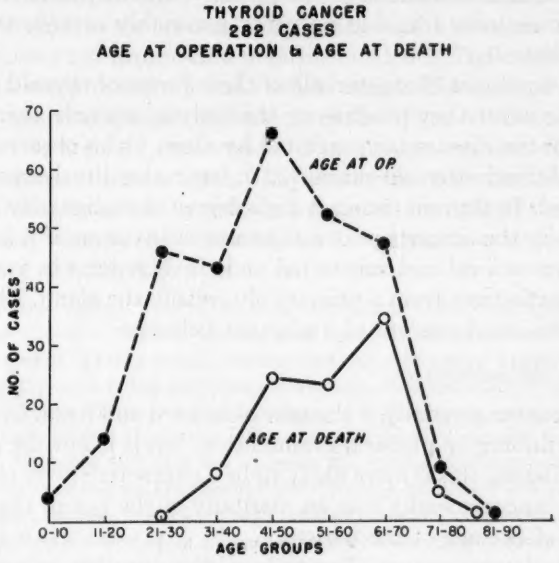

FIGURE 4

multiple foci, there were 12 "mixed," 11 "papillary," 6 "follicular" and 1 "Hürthle-cell," cancer.

A characteristic of "young cancers" occurring in either young or old patients, therefore, seems to be lymphatic spread. As these cancers grow old in a young patient, the characteristic of invasiveness develops, yet even the histologic evidence of invasion when it does occur within the group of young patients is not an infallible criterion of the degree of malignancy of the tumor nor of the propensity for the neoplasm to metastasize distantly.

The "pure" or almost pure form of primary follicular cancer shows other characteristics regarding the variability of its distribution within the body. The primary site is often small and shows little tendency to grow. In early years, it may spread by lymphatics just as papillary cancer does, but when it arises later it shows little tendency to spread to lymphatics. Also it ex-

hibits little capacity for interstitial invasion until later. This is the type of tumor which in middle life and later metastasizes to bone, obviously via the blood stream; and yet even at this time it may show little, if any, invasion at the primary site. This is the tumor which is discovered in older patients because of the occurrence of pathologic fractures, spinal cord compression or the discovery of unusual tumors (with or without associated symptoms) of the sternum, scapula, skull and pelvis or other bones (21). As with the predominantly papillary or mixed forms, the metastatic spread of this form of cancer often is great and out of all proportion to the size or degree of invasiveness of the primary tumor. Moreover the extent of the tumor actually found at necropsy invariably exceeds that found or suspected clinically.

Thus the dominant characteristic of these forms of thyroid cancer, with regard to the effect they produce on the body as a whole, seems to be not the extent of the disease (as suggested by Horn,[2] who observed this paradoxical condition in thyroid cancer (22)), but rather the degree of invasiveness acquired. In thyroid cancer a high degree of malignancy is not determined even by the occurrence of metastases or invasion, if it is agreed that the extensive cervical and substernal node involvement in young patients represents metastases from a primary site within the gland. This is at variance with the usual concept of malignant behavior.

5. *Physical characteristics*

Thyroid cancer generally is thought of as hard and fixed. Of course, such may be the finding on physical examination, but it is not the rule. As with human attributes, this is more likely to be a characteristic of old age. In the case of the cancer, usually it is an attribute of the age of the disease, not necessarily of the age of the patient.

On physical examination alone it is seldom possible to make the diagnosis of thyroid cancer. Any thyroid gland at any age may contain cancer; the cancer may be microscopic or so small that it cannot be seen or felt. When it does attain a size sufficiently large to be palpable, its consistency will vary. Usually it will be "firm," but this will be true of most thyroid nodules. Careful palpation and experience will suggest that it is somewhat irregular and not smooth. Obviously, in this early stage of its development,

[2] Horn stated: "So far as prognosis is concerned, the extent of the disease is more significant than the pathologic type." Others have expressed the same idea but we must recognize that this is not precisely true when we realize how extensive the disease may be in some of these young patients. Our youngest patient had extensive disease in the cervical region and she is apparently well eighteen years later. There are many similar reports in the literature affirming the good prognosis of cancer of the thyroid in this age group, regardless of the extent of the disease, or indeed of the amount and type of therapy employed.

it will not be fixed to the trachea, and the gland itself will move well on deglutition. Fixation of the gland to the trachea and fixation of the gland to adjacent structures, inhibiting movement of the trachea, are likely to be signs of advanced cancer. Occasionally even when the disease, as well as the patient, is young, the tumor will be hard. However, this does not necessarily mean that it is invasive, or that surgical extirpation is impossible. In our series of 282 patients, among the 101 between age 4 and age 40, 18 (18 per cent) had tumors described as hard, including the gland of the youngest patient. Among the remaining 181 patients 40 years of age or over, 79 (44 per cent) had goiters described as hard. About one fifth of the cancers in the younger age group and about one half of the glands in the older age group were described as hard. The majority of thyroid cancers, therefore, are not hard in any stage. The same is true of the palpable soft-part metastases. Usually these are firm but not hard. Some malignant goiters are soft or "cystic." A surprising number of adenomas and cancers are described as "cysts" or "cystic" prior to, and at operation. Perhaps notable among soft tumors are those of the Hürthle-cell variety.

Most thyroid cancers are discrete, easily palpable nodules, and frequently solitary (23, 24, 25).

This matter of the "solitary" nodule requires elucidation. It has been observed already in discussing the origin of thyroid cancer, that most cancers are found in otherwise normal thyroid glands. This is actual physical fact, on the basis of examination of the material at operation and in the pathology laboratory. The incidence of cancer among all such solitary nodules discovered in this manner (which includes cysts, single nodules of nontoxic nodular goiter, single true adenomas and solitary cancers) is between 20 and 30 per cent. However, this does not represent the incidence of cancer among goiters which on physical examination are thought to be solitary nodules. Such an estimate is impossible to make, because it will vary with the ability and experience of the examiner. Any statistical estimate based upon such observations is unreliable. Even the estimate based upon operative and pathologic examination is inaccurate, because of the variability with which the gland is examined at operation and the fact that, even in the laboratory, serial sections are not routinely studied. The incidence figure of 20–30 per cent is sufficiently accurate to constitute the basis for selection of patients for operation, when a competent observer finds what he thinks is a solitary nodule in an otherwise clinically normal gland.

6. *Rate of growth*

Characteristically, thyroid cancer grows very slowly and in this respect its development is similar to that of most other goiters. A change in the rate of growth, however, has great significance. Usually this portends serious trouble, frequently signifying the presence of a Group III cancer. Occasionally a simple nontoxic nodular goiter will grow rather rapidly but seldom, if ever, with the rapidity of a Group III cancer. The physical characteristics of the two differ also, the cancer being hard and fixed. The signifi-

cance of this phenomenon of sudden growth in an existing goiter is worth conjecture from the standpoint of the behavior of thyroid cancer related to its age.

It is important to clarify the term "pre-existing goiter" when applied to this change in rate of growth. Most forms of nodular goiter, malignant included, may be thought of as "existing"; that is, patients present themselves to a physician having a goiter which has been noted for x number of months or years or has never been noted previously. It is simply present and tends to remain the same size or to increase slowly in size under observation. When, quite suddenly, an "existing" goiter begins to grow rapidly (a process usually noticeable during a period of weeks or a few months), the goiter that was present previously is properly designated as "pre-existing." This is the situation which has been observed in over half of the Group III cancers observed in the present series (19 out of 31 cases). Naturally, one associates the development of the very malignant goiter with the previous thyroid tumor. The possibility exists, therefore, that the tumor was a malignant goiter previously, but in a phase of malignancy comparable to a Group I tumor.

7. *Gross appearance*

At operation, the presence of a "nodular" lobe on one side and what appears to be a completely normal lobe on the other (as distinguished from a bulky lobe without obvious nodules) at once arouses suspicion of malignancy. The changes in simple nontoxic nodular goiter, as stated, usually affect the entire gland. It makes little difference whether the involved lobe appears to be multinodular, so long as the other lobe seems normal. Such a lobe might be an irregular but homogeneous neoplasm on cut section. The presence of unusually firm but not definitely calcified nodules, even within a goiter containing multiple nodules in both lobes, must be regarded with suspicion, although in such a gland the likelihood of cancer is remote. It must be recalled, however, that calcification is no guarantee of benignancy. One had better examine and submit such a gland to the pathologist for examination of suspicious areas by frozen section.

One must not be misled by tumors thought to be cysts. Actually, thyroid cysts are not very common. If solitary, they should be construed as neoplasms—adenomas or possible cancers—even though the smooth, spherical, bluish tumor has the appearance of a benign structure. After removal, often the gross appearance of the cut section will suggest the correct diagnosis. Smooth lined cysts containing clear fluid and encapsulated or well defined areas of hemorrhage, recent or old, are obvious. Cyst walls which are thickened at some point, particularly if the configuration of the thickened area is papillary and projects into the cyst cavity, suggest neoplasm, possibly malignant. Masses containing large amounts of colloid and degenerating parenchyma, especially if multiple, probably are simple nontoxic nodular goiters; these often have the appearance and consistency of cysts.

Some nodules are firm, appear solid and meaty, may or may not have a distinct capsule, but appear organized. These nodules may be papillary cancer (single or multifocal), areas of hyperplasia, fibrosis, or thyroiditis, and should be examined by a competent pathologist grossly and by frozen section. Solid reddish tumors, even if soft, suggest Hürthle-cell, papillary or mixed tumors. The tan-colored or yellowish solid growths suggest follicular tumors, either benign or malignant. Usually a frankly malignant neoplasm will be fairly obvious because of its white cut surface, irregularity, grossly invasive nature, and very firm or hard consistency; there is lack of calcium to account for the hardness. Occasionally a very irregular, very firm, possibly partly calcified but generally nonadherent, thyroid mass may be mistaken for a malignant neoplasm.

Usually Group III cancers are obvious. They are large, fixed, invasive, often obstructive, and may contain varying amounts of necrotic tumor which may be mistaken for pus. In fact, an operation may be performed on such a neoplasm, under the impression that it is a suppurative process, for these neoplasms sometimes are associated with fever, elevated leukocyte count and elevated sedimentation rate.

Occasionally, even in what seems to be the most benign sort of nontoxic nodular goiter, a gross area of cancer will be noticed by the surgeon or, more frequently, a small or microscopic focus of tumor will be found by the pathologist when he examines the specimen at operation or later in the laboratory. Failure to detect these cancers at operation is sometimes unavoidable and probably accounts for the very occasional discovery of cancer in patients who previously had partial thyroidectomies for simple nontoxic nodular goiters. We know that the two conditions may co-exist, although very probably not in a cause-and-effect relationship, as already discussed.

8. *Behavior of primary and metastatic thyroid cancer related to variations of form and function*

As has been pointed out, cancer of the thyroid which is predominantly papillary tends to metastasize to lymph nodes, lungs and other soft parts, whereas the follicular type when "pure" or almost "pure" tends to metastasize to bone, except in youth. In this early age group, metastases may be found in nodes and lungs but seldom, if ever, in bone. Metastases to bones seems to be a function of age—in this respect apparently a function of age of the patient (?). As time has passed and experience with the disease has increased it has become evident that primary cancers, considered to be purely one form or another, have shown metastatic forms of a morphologic pattern different from that at the primary site. Such a case in our series was regarded initially as "Grade II adenocarcinoma." Subsequent exami-

nation of tissue from metastatic foci in subpectoral lymph nodes in this individual prompted Dr. Frantz to make the comment that "with the passage of years the tumor has become more and more strikingly papillary." The experience of finding one morphologic type of primary neoplasm and another morphologic type of metastasis in the same patient has become so familiar that it is conceivable that there are no pure papillary or follicular cancers but a single cancer of mixed type. It may be predominantly one or the other, and in general will behave in metastasizing according to the predominant pattern, although metastases of the other type will occur. This point of view will certainly be challenged but it is a plausible concept when the behavior of thyroid cancer is studied carefully.

At the same time that these observations were being made, other interesting variations of form and function between primary and metastatic tumor have been noted. In a group of 20 highly malignant anaplastic neoplasms, there were 2 cases with simple papillary elements in addition to the anaplastic forms which constituted the general and dominant patterns of these tumors. In general, the metastases from these anaplastic neoplasms showed anaplastic metastases; but in one, a metastasis to the liver and another to a lymph node were pure papillary tumor. In another case, a cervical node showed a papillary type of tumor although, later, biopsy of the thyroid gland showed an anaplastic morphologic pattern. It was also noted that metastases from the rapidly growing "benign-morphology" group of neoplasms showed neither anaplasia nor forms more malignant histologically than the original tumor. In the case of the anaplastic tumors, when metastases were present at all (frequently these tumors seemed to grow so fast that they overwhelmed the patient without producing metastases), the majority were of the same anaplastic type but were occasionally of the "benign" type.

One of our patients illustrates this change in morphology which sometimes accompanies increasing malignancy:

M.R. (*P.H. #652604*):[3] A 40-year-old negro maid was first admitted to the Presbyterian Hospital on September 2, 1941, because of a pathologic fracture of the left humerus. On physical examination, it was discovered that she had a large skull metastasis in the left parietal region. Skeletal films showed other areas of metastatic bone destruction in the upper end of the left femur and in the lower end of the right femur. She was found to have a thyroid scar also. Histologic examination of tissue aspirated from the skull tumor suggested that the site of origin of the malignant neoplasm was the thyroid gland. Ultimately it was reported by a girlhood friend that the patient had had "a thyroid tumor" removed in Florida at the age of 5. It was discovered also that she had had a thyroid operation at St. Luke's Hospital in New York City in 1934. The pathology slides of tissue removed at that time became available for study. She is thought to be the subject of the first report of thyroid cancer studied with radioactive iodine. An uptake of about 25 per cent was found in the metastases in the right lower femur,

[3] Case previously reported by Frantz *et al.* (28).

which was greater than the uptake in any other area, including the thyroid gland. Subsequently, she showed spine metastases with cord compression, and also lung metastases. She died rather suddenly in July 1943 with pulmonary edema.

At St. Luke's Hospital in 1934, she was found to have "an encapsulated tumor of the thyroid isthmus." The histo-pathologic diagnosis of this tumor was reported by Dr. Frantz as "carcinoma of the thyroid, adenoma malignum type." Autopsy was performed in 1943, nine years after this tissue was removed. At this time a small, well circumscribed nodule of cancer, 1.2 cm. in diameter, was discovered in the left lower pole of the thyroid gland. The remainder of the gland was essentially normal. This small mass was found to be an undifferentiated cancer which was invading the adjacent normal thyroid tissue. Invasion of a nearby parathyroid gland was also noted. Within the tumor were still visible small thyroid acini similar to those described from a normal area in the gland. Sections from the skull metastasis showed areas closely resembling the tumor removed in 1934. In other areas there was undifferentiated tumor similar to that in most of the metastases. Anaplastic, undifferentiated tumor was found in the other metastases, except in the lower end of the right femur, where it was found to be functional. Here the acini had the histologic appearance of normal gland. There were also small areas of highly differentiated tumor cells similar to those previously described. A large vascular channel was found containing within its lumen tumor cells of various types. A somewhat similar pattern of the tumor was noted in the left femur. A large variety of tumorcells and patterns was observed in the other metastases, which were discovered in the heart, lungs, pleura, diaphragm, liver, adrenals, kidneys, bones and extradural tissues of the thoracic cord. Summarizing the case, Dr. Pappenheimer, who made the histo-pathologic examination of the tissue, stated: "It would seem that the very malignant-appearing form of the tumor must have been a recent development in the story. . . . It is extremely interesting that this femoral metastasis (in the lower right femur) both grossly and microscopically, more closely resembles the normal thyroid than did the metastases in any other lesion."

Apparently this is an instance of the development of either an undifferentiated, anaplastic thyroid neoplasm from a long-standing, well differentiated adenoma malignum, or of another, different, neoplasm in the same gland. It shows in addition the extreme pleomorphism which these tumors my exhibit when they are transferred to other sites and new environments. Some of these forms, in bone in particular, have the appearance of normal gland. The striking resemblance between this behavior and that of malignant thyroid tumors transplanted to, and grown experimentally in animals, is apparent (26). It is to be noted that this tendency to grow more aggressively at the primary site and yet to produce distant metastases which seem like reversions toward more nearly benign forms is a characteristic of the neoplasm in older individuals and in older tumors.

9. *Function in primary tumors and in metastases*

Of all the primary tumors exhibiting a capacity for function the only ones with any appreciable uptake were in patients between 4 and 43 years of age. The tumors of 32 patients in this age interval were studied. There was "very slight uptake" in 3, "slight uptake" in 3, and "good uptake" in 3. There was "no uptake" in 23. "Very poor uptake" was recorded in the

primary tumor radioautographs in 4 out of 28 glands in patients beyond this age, and "no uptake" in the other 24. On the other hand, in the bone metastases of 8 of the latter group of patients the uptake was good or high. In the bone metastases of both young and old patients, the growth showed a greater capacity for function, when any was present, than in any of the primary tumors. This characteristic appears to fit in with the clinical and experimental concept that under different environmental conditions, transplanted thyroid cancer can revert toward functional and organized tissue, *i.e.*, normal gland (27–30).

DISCUSSION

An etiologic relationship between nonmalignant goiter and thyroid cancer has not been conclusively established. Currently it is generally assumed that such a relationship exists. The malignant potentiality of any thyroid nodule has been stressed in clinical teachings about goiter.

The assumption that cancer develops from these simple nonmalignant goiters is derived chiefly from the gross and histologic similarities between them and from the association of the two in the same gland. Thyroid cancer is uncommon, however. Goiter, on the other hand, is very common. By far the majority of goiters are, and always will be, benign. Except for the possibility that such a goiter might be malignant, there are actually few valid reasons for operating upon it, unless there is threatened or actual compromise of the airway, or unless cosmetic improvement is desirable. The concept of *prevention* of cancer or of toxicity by the prophylactic removal of nodular goiters loses much of its strength upon careful analysis of long-term clinical studies, unless one is prepared to advocate total thyroidectomy in every case. This is obviously an impossible undertaking.

A rational and more realistic approach would be to learn enough about the natural histories and characteristics of the various types of goiter so that the dangerous ones might be identified clinically, at least tentatively. It would be hoped also that some benign characteristics frequently and closely associated with malignant change might be found so consistently in some glands that sound prophylactic surgical or other measures against the development of cancer could be employed. Thus there would be greater discrimination in the selection of patients for surgery and a reduction in the number subjected to this form of therapy. Such an attempt has been made on the basis of the study here reported.

The influence of therapy was not evaluated in terms of histologic types of tumors. It was assumed that every surviving patient still has the disease, because neither the type nor the amount of treatment appeared to be the determining factor in the outcome. The present survey, therefore, is merely an interim appraisal of observations made up to this time. Thyroid cancer

shows too many variations in behavior from that which we expect a malignant neoplasm to exhibit, to study it in any other way. As we learn more about its behavior we shall have a firmer basis upon which to report results of therapy.

Under the microscope of an experienced pathologist familiar with thyroid disease the histologic characteristics of malignant goiter are usually sufficiently apparent to make the diagnosis, even from a frozen section. To employ solely the histologic appearance of the tumor as the basis for prognosis and outcome, however, has probably led to most of the confusion which has existed in attempting to evaluate the effects of treatment of thyroid cancer. The histologic classifications used have been grouped in such a manner that certain forms have been considered relatively benign, others more malignant and still others highly malignant. They have been so graded. The papillary cancer has been considered a relatively benign neoplasm. In our studies it was found that the distribution of papillary cancers was fairly uniform throughout the various age groups; however, few of the young patients with these tumors have died, but many of the older patients have succumbed. Reports are beginning to appear in the literature attesting the fact that many papillary cancers are malignant, invasive, and incapable of being completely eradicated.

The relationship of age to benignancy and malignancy is being noted also, the observers finding it difficult to reconcile the poor results in older age groups with the histologic patterns supposed to be indicative of a relatively benign tumor.

Our studies suggest that these malignant neoplasms have lives of their own, so to speak. They appear to start as relatively benign growths, gradually becoming more malignant with age. This transformation is not one of a benign to a malignant state, but a progression in malignancy from the beginning, starting with a state analogous to that of a harmless parasite and developing into one of the most highly malignant neoplasms known, the Group III anaplastic cancers. These are fatal, usually within weeks or months from the time they are recognized.

Nothing in the present study leads to the conclusion that benign neoplasms become transformed into malignant ones. Although they may be found together frequently, they usually develop in different parts of the gland, often at different times. On the other hand, the evidence is convincing that once a malignant neoplasm develops, it becomes more aggressive when the critical point of malignancy is reached. In the over-all pattern in our series of thyroid cancers, this point appears to be when the patient is nearing the age of 40. In individual cases it appeared to vary according to the age at which it originated and the length of time it had existed.

The most intriguing patients, and those from whom we expect to learn

the most, are the young ones. Knowing the histologic types, the associated pathologic changes in the gland, the approximate times at which the disease began, the sites and approximate extent of the disease and the probability of its complete or incomplete removal or destruction, significant data from this group should become available in another fifteen or twenty-five years, regarding the nature of thyroid cancer.

An apparent exception to this concept of the association of aging with degree of malignancy, is the very young child in whom the cancer is overwhelmingly malignant. There have been no children with disease of this severity in our group, and yet it is known that such cases do occur occasionally. We have seen disease in young children and adolescents which seemed to be very aggressive and extensive but which, unlike Group III cancer, has been arrested by surgery and radiotherapy. Aside from the still unexplained common observation that high degrees of malignancy often occur in the very young, there is little that is factual to say about this phenomenon. One might liken it to the antithesis of the maternal protective immunity conferred upon the new born infant. In the case of thyroid cancer such a speculation becomes somewhat more tenable if it is recalled that the disease probably originates most frequently during the childbearing age, and that in children the sex incidences of thyroid cancer approximate equality more nearly than at any other period during the life span. In any event, this apparent exception to the usual behavior of thyroid cancer is so limited in its age level and frequency of occurrence that it is necessary to seek an explanation rather than abandon the entire concept.

It is well known also that some thyroid cancers in elderly patients behave benignly, although the number is far fewer than in young patients. The natural history of thyroid cancer is usually so long that one sometimes wonders whether it does not always begin in youth. This seems most unlikely. We have probably been able to establish the age at onset of thyroid cancer very closely in the 2 patients represented in Figure 3. The glands of these patients were very carefully explored at both operations, so we know with almost complete certainty that one cancer developed after the age of 23 and the other after the age of 25 and probably more nearly at the age of 30. In older patients with relatively benign cancers one explanation, therefore, might be that the growth itself develops late in life and possesses the characteristics of a young cancer.

Carrying this concept of increasing malignancy with age of disease to its logical conclusion, one is led to speculate upon a possible origin of the very malignant Group III thyroid cancers. The old-age level at which these neoplasms occur, the high proportion of pre-existing tumors suddenly growing rapidly, the occasional "benign morphology" patterns found in their metastases, and the behavior of experimentally transplanted tumors of this

type in animals, give reason for thinking that these cancers may simply be an expression of increasing malignancy associated with increasing age of a previously existing neoplasm of a lower degree of malignancy, rather than the sudden development of an altogether new, highly malignant neoplasm from normal gland tissue.

It seems to this author that the concept of increasing malignancy is much more consistent with the observed behavior of thyroid cancer than the concept of multiple malignant tumors, each with its own degree of malignancy. The pathologist affirms that a highly malignant tumor springs from a benign one, with attendant changes in morphology ranging from the most highly organized, orderly, identifiable patterns to the most bizarre and least recognizable that one can imagine; at the same time he denies that a neoplasm possessing all of these malignant characteristics is itself incapable of these changes. It is an inconsistency which this writer has difficulty in resolving. We are so accustomed to seeing only the late stage of cancer in its inexorable progress through a terminal malignant phase toward a fatal outcome, that it is very difficult to conceive of this ever having been a reversible process; and yet such a possibility is suggested by the behavior of thyroid cancer.

It has often been said of thyroid cancer that, despite its apparently bizarre behavior, it is not really fundamentally different from other malignant neoplasms. The converse of this must be true also. Because of its long life-span, it is seen developing in slow motion as it were. This neoplasm can be followed through earlier stages of development than is possible with any other known malignant tumor. It is for this reason that, despite its relatively infrequent occurrence among all human cancers, it is such an important one to study.

SUMMARY

From clinical and statistical studies of 282 cases of thyroid cancer, 513 cases of nonmalignant nodular goiter and from other statistical studies of the incidence of simple nodular goiter, the following statements regarding the origin, characteristics and behavior of thyroid cancer seem valid:

Cancers are found most frequently in otherwise normal glands.

Benign and malignant neoplasms exist in an unusually high incidence in the same gland concurrently, or at different times and at different sites. Cancer probably is cancer from the beginning and not a transformation.

Simple nodular goiter rarely precedes cancer.

Highly malignant histologic types are seldom found before the age of 39.

Metastases, morbidity and mortality increase sharply after the age of 39.

The type and extent of treatment have far less influence on prognosis than age of the disease and age of the patient.

Prognosis for cancer in the young is favorable, whatever the local findings.

Prognosis for cancer with similar local findings later in life is unfavorable.

Deaths occur in the young usually only after long duration of the disease.

Deaths occur in the elderly often after long duration of the tumor, and usually relatively much sooner following diagnosis than in youth.

Acknowledgments

It is with gratitude that the author acknowledges the assistance and cooperation of the other members of the thyroid group at the Presbyterian Hospital, who gave permission for inclusion of a number of their patients in this study. Some of the points of view expressed here are not shared by all the members of this group. This is probably as it should be.

To Dr. Virginia Kneeland Frantz who, as a pathologist, also possesses a rare and highly desirable combination of clinical knowledge of this disease, a sympathetic understanding of the patient as a human being, and a critical knowledge of his disease in the laboratory, the author acknowledges an especial debt of gratitude and appreciation, shared it may be added, by every other member of the thyroid group.

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CANCER OF THE THYROID*†

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INTRODUCTION

SATISFACTORY treatment of cancer of the thyroid depends not upon static morphologic standards but on a dynamic concept based upon an understanding of the biologic characteristics of these tumors. The physician faced with the problem of thyroid malignancy needs the answers to questions regarding the functional and biologic potential rather than a microscopic description of dead tissue. Of itself, the histology of a tumor has no value unless it can be utilized to predict how the cells of the tumor will act.

This concept of cancer as living tissue is particularly important in any study of thyroid cancer because of the biologic and histologic variability of the tumors, the protean manifestations of the disease, the endocrinologic aspects of many of the tumors and the availability of isotopic iodine for use in study and treatment.

The present study consists in the evaluation of 190 cases with an established diagnosis of cancer of the thyroid which were admitted to the Massachusetts General Hospital from 1931 through 1951. The objective was the accumulation of information which would help to direct our therapy along rational lines, based on the biologic characteristics of the various types of tumors.

CLASSIFICATION

One of the difficulties in evaluating reports on cancer of the thyroid has been a lack of a uniform classification of the disease. It is well recognized that there are at least three and possibly four major divisions into which cancers of the thyroid may be reasonably grouped, on the basis of both

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biologic characteristics and pathologic criteria. It has also been recognized, however, that the general classification into papillary carcinoma, adenocarcinoma, and anaplastic carcinoma has not been completely satisfactory; and there has been little agreement in terminology in the various subdivisions which have been described in the past. The use of strict morphologic criteria for the classification of tumors frequently fails to take into consid-

TABLE 1. CLASSIFICATION OF THYROID CANCERS IN PATIENTS ADMITTED TO THE MASSACHUSETTS GENERAL HOSPITAL (1931–1951). SEX AND AGE INCIDENCE, FIVE-YEAR SURVIVALS AND DEATHS

The five-year survival percentage in this table is a simple arithmetical calculation; the cumulative five-year survival rate for each type, a more significant representation of the data, may be found in Tables 3, 4 and 5 and in Figure 2.

	Number of cases	Sex		Age (yrs.)		5-Year survivals		Deaths	
		M	F	Average	Range	Number	Per cent	Number	Per cent
I. *Differentiated*									
A. Follicular carcinoma	45	10	35	51.6	19–83	16	35	15	33
1. Localized carcinoma in follicular adenoma	19	4	15	52.1	33–83	7	37	5	26
2. Follicular adenocarcinoma	26	6	20	51.2	19–78	9	35	10	39
B. Papillary carcinoma	89	26	63	44.7	11–76	38	43	28	31
II. *Undifferentiated*	45	20	25	60.5	32–80	5	11	32	71
A. Small-cell (diffuse and compact)	33	11	22	60.1	34–80	4	12	23	70
B. Giant-cell	12	9	3	61.6	32–75	1	8	9	75
III. *Miscellaneous*									
A. Epidermoid carcinoma	5	4	1	65	56–72	0	0	5	100
B. Fibrosarcoma	3	0	3	62	37–78	0	0	2	66
C. Lymphoma	2	0	2	70	64–76	0	0	1	50
D. Hürthle-cell carcinoma	1	—	1	29	—	0	0	0	0

eration the biologic characteristics of the various types of cancer, and it is this biologic individuality which is of the greatest importance to the physician who is attempting to treat the disease on a rational basis. Nonetheless, some form of classification must be used or complete disorganization will result.

The classification which we present in this report appears in Table 1. It is almost identical with that proposed by Warren and Meissner in the Atlas

of Tumor Pathology (Section IV) published under the auspices of the Armed Forces Institute of Pathology (1).

The general adoption of this classification by Warren and Meissner is to be recommended, since it employs a terminology which is satisfactory, accurate and descriptive. It is important, however, to recognize the limitations of any arrangement of this type. In comparing the biologic characteristics of our series of thyroid tumors with the microscopic classification, it is apparent that there is considerable overlap among the categories. For example, 7 of the papillary tumors showed distant metastases which clinically and functionally resembled follicular carcinoma, and at least 1 of the localized carcinomas in a follicular adenoma metastasized directly to regional nodes. Other examples could be cited but, in general, the classification of the tumors by these histologic criteria compared reasonably well with any classification of this particular series based on similarities in biologic and functional characteristics.

Photomicrographs of typical tumors from these categories are shown in Figure 1.

The differentiated cancers of the thyroid have two main subdivisions: the papillary carcinomas and the follicular carcinomas. The papillary carcinomas require little further explanation. Microscopically these tumors reproduce to some extent the normal architecture of the thyroid but demonstrate many papillary infoldings and proliferations which have long been recognized as a distinguishing feature of this type of cancer. The clinical characteristics of the papillary type will be discussed further under a separate heading. The term follicular carcinoma has been adopted for many reasons. Some differentiation of this tumor into typical thyroid follicles is almost always apparent in histologic sections. From the point of view of the accepted definition of the word follicular, it is preferable to either alveolar or acinar—terms which have been applied to this type of cancer in the past. The term follicle refers to a closed epithelial sac, whereas acinus and alveolus have been used interchangeably for the saccular or tubular termination of the duct of a racemose gland. It seems reasonable to adopt the term follicular carcinoma as the nomenclature. Within this group of follicular carcinomas, however, it has long been apparent that there are at least two different types of tumors, if one considers the classification on the basis of biologic characteristics. Some of these tumors have a typical micro-

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FIG. 1. Photomicrographs illustrating the microscopic criteria for the classification used in Table 1. **A.** Localized carcinoma occurring in a follicular adenoma. **B.** Follicular adenocarcinoma. **C.** Papillary carcinoma. **D.** Undifferentiated carcinoma, small-cell (diffuse) type. **E.** Undifferentiated small-cell (compact) type. **F.** Undifferentiated carcinoma, giant-cell type.

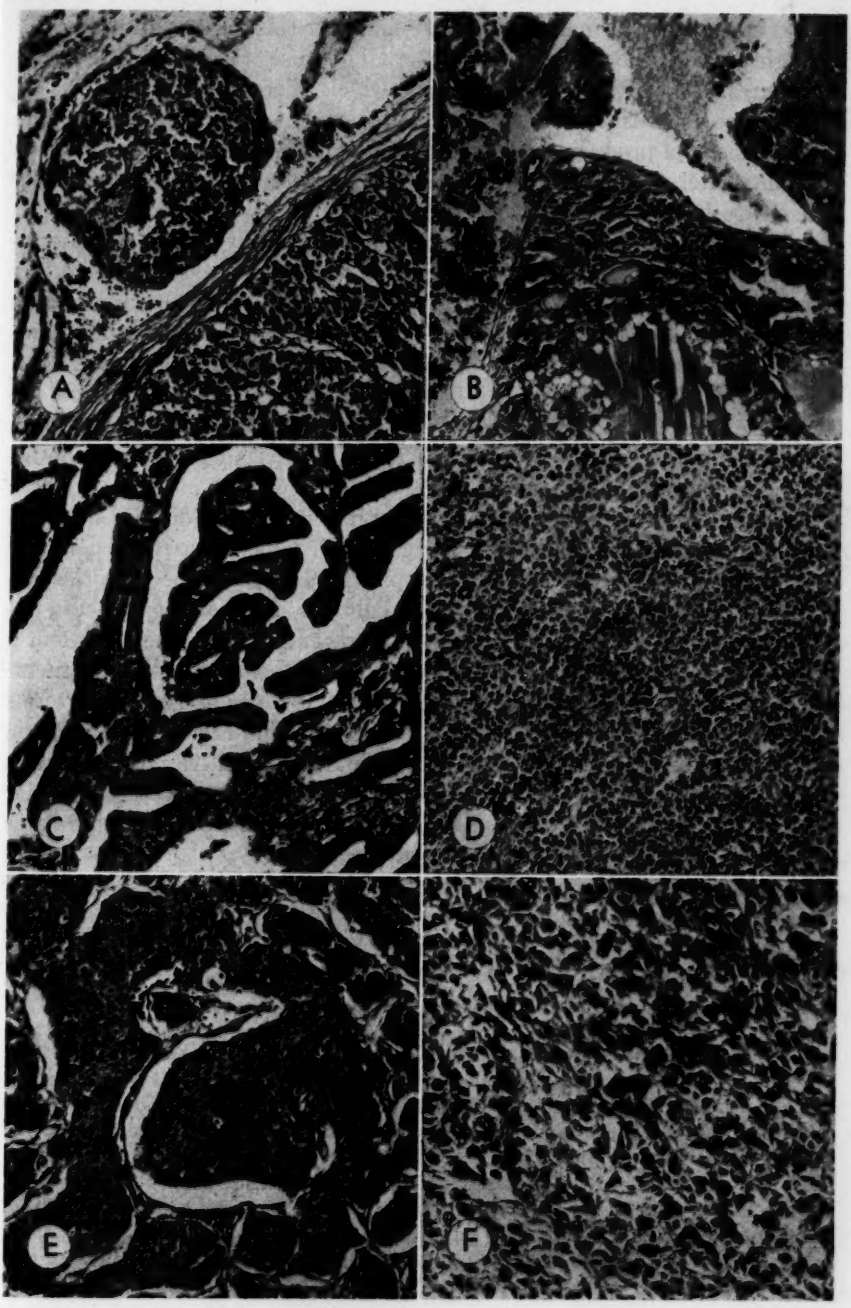

FIGURE 1

scopic appearance of malignancy, and clinically this group will ordinarily be highly invasive locally and may be lethal because of invasion of adjacent structures. In addition, there is a type which microscopically has few, if any, of the established criteria of malignancy but does have the biologic characteristic of producing distant skeletal or pulmonary metastases which may ultimately bring about death, even though the primary tumor never goes on to local invasion beyond the limits of its capsule. Admittedly, in many cases it is difficult to decide into which of the sub-groups an individual tumor belongs. With these obvious limitations, however, we have further attempted to subdivide the main group of follicular carcinomas into the localized carcinomas arising in a follicular adenoma and into the adenocarcinomas which show the typical invasive characteristics of cancer both microscopically and grossly. By the use of this type of classification the term malignant adenoma, which by definition is paradoxical, has been avoided. Further discussion of these types of thyroid cancer will be included in a subsequent section.

The undifferentiated cancers of the thyroid have been divided into two groups, the small-cell type and the giant-cell type. These divisions are made strictly on the basis of microscopic characteristics, because the biologic characteristics of these tumors are almost identical. Again these undifferentiated cancers will be considered further in a subsequent section.

Under a third main group have been included the unusual malignant tumors of the thyroid which have occurred in this series of cases. The terms epidermoid carcinoma, fibrosarcoma and lymphoma are in such common usage as to be self-explanatory. The single Hürthle-cell carcinoma in this series has also been placed under this main heading. The biologic behavior of this tumor, however, suggests that, had we more experience, this type should be classified as a follicular carcinoma.

As may be seen from the data presented in Table 1, there is a striking difference in the sex and age incidence, the five-year survival rate, and the frequency of the various types of tumor. These differences will be considered subsequently.

METHODS

1. *Basis of entry into study.* All cases with a clinical or pathologic diagnosis of thyroid cancer in the Massachusetts General Hospital between 1931 and 1951 were reviewed. Both the clinical data and the pathologic sections were re-evaluated and the diagnosis of thyroid cancer confirmed before inclusion in the study. Patients entered the study on the date of the first procedure in the Massachusetts General Hospital that provided a histologic diagnosis. Some of the cases had been treated before entry to this hospital. The histologic diagnosis was in some cases made in other hospitals: in these instances, entry into the study was the date of admission.

2. *Follow-up.* Whenever the hospital record did not provide the date and cause of death for a patient, recent information about his subsequent course was sought by

letters to the patient, his family, his personal physician or the municipal authorities. In preparing the mortality table all patients were classified as either "dead" or "lost to follow-up." The date of the last information about a patient is his date of entry into the category termed "lost to follow-up." Column 3 in Tables 3, 4 and 5 presents a frequency distribution of the duration of follow-up.

3. *Methods of presenting data.* Tables 3, 4 and 5 are mortality tables calculated in a standard manner (2, 3). The legend under Table 3 describes the method of calculation. There are distinct advantages inherent in this method:

a. Complete information about the period of follow-up is provided, as just described.

b. Interval survival rates are readily calculated from the cumulative survival rates. The cumulative survival rate ranging from entry into the series to year B, divided by the rate to year A, gives the probability of surviving from year A following entry to year B.

c. "Five-year cure rates" are usually calculated only on the basis of patients followed for five years or longer. Therefore, patients are discarded who provide information on the probability of surviving only from the time of entry into the study through the fourth year, because of "insufficient follow-up." By using the data that are usually discarded, it is possible to make a better estimate of the proportion of all patients who will survive from the end of the fourth to the fifth anniversary of entry into the study. By calculating survival rates for each time period, patients do not need to be discarded until their follow-up no longer provides information. By accumulating these "period survival rates" (the probability of surviving one period multiplied by the probability of surviving the next, and so on) one arrives at a probability for five-year survival that is a better estimate than the one calculated only on the basis of cases followed for five years or more.

d. The mortality-table technique has further advantages for other types of data; it was thought wise to adopt a technique which would be useful for comparison with other series.

GENERAL CONSIDERATIONS

Certain generalizations in regard to cancer of the thyroid may be made on the basis of the data presented in Tables 1 and 2 and in Figure 2.

It is apparent that all the forms of differentiated cancer of the thyroid are primarily diseases of women. This sex difference is not so apparent in the undifferentiated group, which apparently follows a more random sex distribution.

TABLE 2. THREE MAIN GROUPS OF THYROID CANCER ANALYZED AS TO PRE-EXISTING GOITER, PRESENCE OF DEMONSTRABLE METASTASES AT THE FIRST ADMISSION, SURGICAL RESECTABILITY OF THE PRIMARY TUMOR, AND HOSPITAL MORTALITY

Type of cancer	Total number	Pre-existing goiter (more than 3 years)		Number of cases with metastases at first admission		Resectability		Hospital mortality	
		Number	Per cent	Regional	Distant	Number	Per cent	Number	Per cent
Papillary carcinoma	89	28	32	54	7	79	88	1	1
Follicular carcinoma	45	27	60	8	20	34	75	1	2
Undifferentiated carcinoma	45	10	22	18	12	12	27	5	11

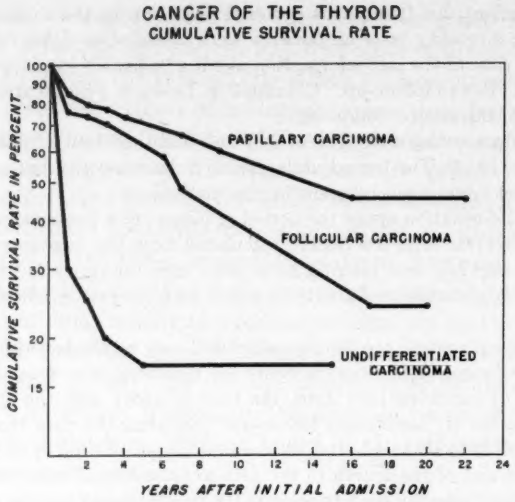

FIG. 2. Cumulative survival rates in thyroid cancer, by histologic classification. The ordinate (cumulative survival rate) is plotted logarithmically. The curve has the same slope in all periods that have equal period survival rates, regardless of the cumulative survival rate at a given period.

With the exception of papillary carcinoma, cancer of the thyroid is a disease of the middle and later spans of life. Papillary cancer, however, has a relatively high incidence of occurrence in the earlier decades of life and has been found even in prepubertal children in this series.

There was a striking difference in mortality between the various types of cancer. As might be expected the differentiated form was much less lethal than the undifferentiated type; in the latter instance only 11 per cent of the patients have survived five years or longer. On the other hand, among the more differentiated tumors appreciable numbers of patients in this series have already survived five years and a relatively smaller proportion have died since their initial admission.

There are many statistical fallacies, however, in calculating five-year survivals out of a limited group of patients who had the opportunity to survive five years; therefore, in Figure 2 cumulative survival curves have been plotted on the basis of the data shown in Tables 3, 4, and 5. This type of calculation and graphic representation of the data should give a much more accurate picture of the survival rate of patients with a specific type of disease and therefore this figure should be of greater interest and significance in obtaining a proper understanding of the characteristics of the various types of thyroid cancer. It is apparent from Figure 2 that there is a striking difference between the prognosis of papillary carcinoma and that of

TABLE 3. MORTALITY IN 89 CASES OF PAPILLARY CARCINOMA OF THE THYROID FOLLOWING INITIAL DIAGNOSIS AT THE MASSACHUSETTS GENERAL HOSPITAL DURING THE PERIOD 1931–1951

1	2	3	4	5	6	7
Time period ending	Deaths	Lost to follow-up	Patients entering time period	Patients at risk in time period	Time-period survival rate (%)	Cumulative survival rate (%)
1 yr.	14	5	89	86.5	84	84
2 yrs.	4	7	70	66.5	94	79
3 yrs.	1	11	59	53.5	98	77
4 yrs.	1	9	47	42.5	98	73
5 yrs.		4	37			
6 yrs.		8	33			
7 yrs.	2	7	25	21.5	91	66
8 yrs.		4	16			
9 yrs.	1	2	12	11	91	60
10 yrs.			9			
11 yrs.		1	9			
12 yrs.		2	8			
13 yrs.			6			
14 yrs.		1	6			
15 yrs.		1	5			
16 yrs.	1		4	4	75	45
17 yrs.			3			
18 yrs.		1	3			
19 yrs.		1	2			
20 yrs.			1			
21 yrs.			1			
22 yrs.		1	1			

Column 1. "Time period ending at 2 years" means the 6-month period preceding the second anniversary of entry into the study. The only time periods shown are those during which a patient died from thyroid cancer or was "lost to follow-up."

Column 2. When a blank occurs, there was no death in the time period.

Column 3. See paragraph headed "Follow-up" in the text.

Column 4. Patients entering the preceding time period, less the deaths and losses in the preceding period.

Column 5. Column 4, less one half of Column 3. Calculations are only for time periods in which there was a death from cancer.

Column 6. Column 2 divided by Column 5 and subtracted from 100. In time periods in which there was no cancer death the survival rate is 100 per cent, but this is omitted for clarity.

Column 7. The probability (in per cent) of surviving from the time of entry into the study to the time in Column 1. It changes only in the periods in which there was a cancer death. Omitted figures are the same as the Column 6 probability. Calculations are made by multiplying the cumulative survival rate of the preceding time-period (Column 7) by the current time-period survival rate (Column 6).

TABLE 4. MORTALITY IN 45 CASES OF FOLLICULAR CARCINOMA OF THE THYROID FOLLOWING INITIAL DIAGNOSIS AT THE MASSACHUSETTS GENERAL HOSPITAL DURING THE PERIOD 1931–1951 (SEE NOTES TO TABLE 3).

1	2	3	4	5	6	7
Time period ending	Deaths	Lost to follow-up	Patients entering time period	Patients at risk in time period	Time-period survival rate (%)	Cumulative survival rate (%)
1 yr.	11	2	45	44	76	76
2 yrs.	1	5	33	30.5	97	74
3 yrs.	1	4	27	25	96	71
4 yrs.		1	22			
5 yrs.		4	21			
6 yrs.	3	2	17	16	81	58
7 yrs.	2		12	12	83	48
8 yrs.			10	10		
9 yrs.		2	10			
10 yrs.		3	8			
11 yrs.			5			
12 yrs.		1	5			
13 yrs.			4			
14 yrs.		1	4			
15 yrs.		1	3			
16 yrs.			2			
17 yrs.	1		2	2	50	24
18 yrs.			2			
19 yrs.		1	2			
20 yrs.			1			

undifferentiated carcinoma. Perhaps the most interesting feature of this particular graph is the biphasic character of the survival curve plotted for the follicular carcinomas. If one examines the data carefully it is apparent that over half of the deaths from follicular carcinoma occurred within the first two years after the diagnosis had been established. Most of these deaths resulted from local invasion by the cancer. Then there was a latent period for another two and a half years, during which none of the patients with follicular carcinoma died. At about the five-year point another series of deaths occurred and continued to occur over the subsequent decade. This would suggest that there are two different types of cancer under this general heading of follicular carcinoma, and this impression is borne out by a more careful individual analysis of these cases. This problem will be discussed at greater length under a subsequent heading.

There is nothing in the data presented in this report which has any bear-

TABLE 5. MORTALITY IN 45 CASES OF UNDIFFERENTIATED CARCINOMA OF THE THYROID FOLLOWING INITIAL DIAGNOSIS AT THE MASSACHUSETTS GENERAL HOSPITAL DURING THE PERIOD 1931–1951 (SEE NOTES TO TABLE 3)

1	2	3	4	5	6	7
Time period ending	Deaths	Lost to follow-up	Patients entering time period	Patients at risk in time period	Time-period survival rate (%)	Cumulative survival rate (%)
1 yr.	30	4	45	43	30	30
2 yrs.	2		11	11	82	25
3 yrs.	2		9	9	78	20
4 yrs.			7			
5 yrs.	1		7	7	86	17
6 yrs.		2	6			
7 yrs.			4			
8 yrs.		1	4			
9 yrs.		2	3			
10 yrs.			1			
11 yrs.			1			
12 yrs.			1			
13 yrs.			1			
14 yrs.			1			
15 yrs.		1	1			

ing on the incidence of thyroid cancer in the population at large, nor is there any attempt to evaluate the incidence of cancer in nodular goiter or in solitary nodules of the thyroid. Nonetheless, some of the information presented in Table 2 is of interest in regard to the pathogenesis of thyroid cancer. It is striking that a large percentage of these patients had pre-existing thyroid disease, and this information has been presented in a simplified form by reporting the number of patients who were known to have a goiter for more than three years before the diagnosis of thyroid cancer was first established. In the group of follicular carcinomas almost two thirds of the patients were known to have pre-existing thyroid disease three years or more before the diagnosis of thyroid cancer was established. Even in the papillary group, a third of the patients similarly evaluated had pre-existing thyroid disease, and the inference would be that in regard to the differentiated types of thyroid cancer, either the malignant process had existed for many years before the diagnosis was made, or it arose in a thyroid already diseased. In the undifferentiated group a much smaller percentage of patients had a long-standing history of goiter.

A large percentage of the total series of thyroid cancer showed demon-

strable metastases at the time the diagnosis was established. In the papillary group, with few exceptions, these metastases were characterized as regional, *i. e.*, the spread had occurred only to the lymph nodes in the neck or upper mediastinum. Therefore one might expect that papillary cancer would be more amenable to surgical resection, and that impression is borne out by the relatively high survival rate in this group. The follicular carcinomas, although locally resectable in almost as high a percentage of patients as the papillary carcinomas, were not surgically curable in almost half the cases even at the time of initial admission, because of distant metastases to the skeletal system or to the lungs. The undifferentiated group of cancers showed a high percentage of both regional and distant metastases and the degree of local invasion was apparent from the fact that only 27 per cent of this group were considered surgically resectable from the point of view of a direct attack on the primary tumor.

There was a low hospital mortality in the entire group, since it was possible in a great majority of the cases to offer enough palliation so that the patient could be discharged, even though the disease was hopelessly incurable. It is important to note this very low hospital mortality because it is apparent that, in this group at least, very few patients died in a hospital and therefore a survey of the autopsy material at this hospital would give a false impression of the actual incidence of thyroid cancer.

The miscellaneous group of relatively rare thyroid cancers contained too few cases to warrant any conclusions, but a few observations are pertinent. In the small group of 5 epidermoid carcinomas, no patient survived more than one year after the diagnosis was made. The inference is, therefore, that epidermoid carcinoma arising in the thyroid is a highly malignant lesion and carries a poor prognosis. All the patients with lymphomas and fibrosarcomas which apparently arose in the thyroid died of their disease and the 1 patient with Hürthle-cell carcinoma is still living with slow-growing skeletal metastases.

PAPILLARY CARCINOMA

The papillary carcinomas comprise the largest number of thyroid cancers—almost half of the entire series (Table 1). They also have less malignant potential than any other group, inasmuch as the cumulative survival rate of this group is appreciably higher than in any other type of thyroid cancer (Fig. 2), distant metastases are relatively rare (Table 2), and the whole pattern of growth is relatively leisurely in nature. Biologically its behavior follows a closely prescribed pattern, with early metastases to the regional lymph nodes but with only rare instances of distant blood-borne metastases. It is this type of leisurely metastasis to the cervical chain of lymph nodes that formerly was called "aberrant thyroid tissue." Although

the disease may be entirely localized to the thyroid at the time the initial diagnosis is made, many of the cases are brought to attention by the presence of metastatic nodules in a cervical chain of lymph nodes rather than by a palpable mass in the thyroid. As has been mentioned, distant metastases from papillary carcinomas of the thyroid are uncommon, but lungs or bones may be involved. Such occurred in 7 cases out of the total number of 89 papillary carcinomas. It is possible that in these rare instances of distant metastases there may have been an admixture of follicular elements. This impression is substantiated by the fact that one of these patients with diffuse pulmonary metastases showed a remarkable clinical improvement and x-ray regression following the administration of I^{131} subsequent to total thyroidectomy.

In Figure 3 the three major types of thyroid cancer have been broken

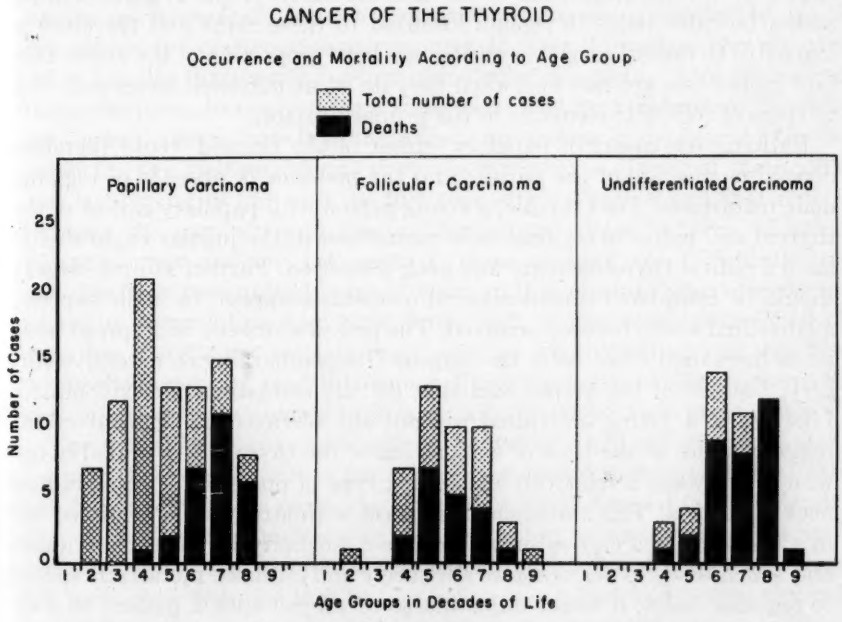

FIG. 3. The incidence of the three main groups of thyroid cancer, according to decades of life. Deaths from cancer are similarly treated according to the age at which the diagnosis was established.

down according to the age incidence and the mortality from the disease in each age group. This analysis of the papillary tumors is striking, inasmuch as it appears that this type of cancer has a different potential in the old than in the young. Although a high proportion of the total group with

papillary tumors occurred in persons in the first four decades of life, only 3 patients who contracted the disease under the age of 50 have died as a result of this cancer. All the remaining patients who died of the disease were more than 50 years of age at the time the diagnosis was established. This is an unusual observation, inasmuch as most other types of cancer are more malignant when they appear in the young. These data substantiate similar observations made by Crile (4) in regard to the malignant potential of cancer of the thyroid relative to age.

With these data available, certain generalizations in regard to papillary cancer of the thyroid are permissible. It is a disease which occurs in almost every decade of life but is, with rare exceptions, the only cancer of the thyroid which occurs in the first four decades of life. There is distinctly greater mortality from this disease if it is contracted over the age of 50. Papillary cancer of the thyroid tends to metastasize early to the regional lymph nodes, but also tends to remain localized to these areas and therefore is amenable to radical surgical excision in a high proportion of the cases. Distant metastases are rare and when they do occur may well be a result of a mixture of follicular elements in the primary tumor.

Rational treatment of papillary cancer of the thyroid would therefore depend on the age of the patient and the presence or absence of regional node metastases. For example, a young person with papillary cancer of the thyroid and palpable regional node metastases in the jugular chain should have a radical thyroidectomy and neck dissection. Further radical surgery should be considered if contralateral metastases appear, or if the superior mediastinal nodes become involved. The presence of even widespread node metastases should not deter the surgeon from embarking on extensive surgery, because of the known fact that distant metastases are uncommon. Likewise in a young individual without any obvious involvement of the regional nodes at the time of exploration of the thyroid it is probably unwise to carry out a relatively mutilating type of operation such as radical neck dissection. This statement may meet with strenuous objections, but in a disease which carries such a very low mortality in young individuals and which tends to demonstrate a leisurely and localized metastatic spread to regional nodes, it seems unjustifiable to subject such a patient to a so-called prophylactic regional node dissection.

In older individuals, however, the situation would appear to be different. Mortality from the disease when it occurs over the age of 50 is such that one could with justification advocate radical dissection of the regional nodes at the time of the initial resection of the thyroid tumor, regardless of whether or not these nodes were clinically involved with cancer. In view of our experience with a case of papillary cancer in which extensive pulmonary metastases responded remarkably well to the administration of

radioactive iodine (I^{131}) it would seem justifiable to administer this isotope for the treatment of distant metastases, even though the initial tumor was microscopically papillary in type and showed no appreciable uptake. From all the information available in this series of 89 cases of papillary cancer of the thyroid, this is the type of cancer which is actually curable in a large percentage of cases, provided a rational approach to the disease is undertaken and persistent attempts are made to eradicate local metastases whenever they appear.

FOLLICULAR CARCINOMA

Under the heading of follicular carcinoma have been grouped all those cancers of the thyroid in which there was microscopic evidence of some degree of reproduction of follicular pattern. Microscopically these showed all degrees of malignancy, ranging from the tumors which would be considered benign microscopically were not distant metastases demonstrable, up to the obviously invasive adenocarcinomas. If these thyroid cancers are considered under the general heading of follicular carcinoma there are certain facts which can be evolved from these data. The sex incidence of this cancer shows that it is more than three times as common in the female as in the male, the age incidence shows that it is primarily a disease of the middle and later spans of life, and the five-year survival rate shows that it falls between the papillary and the undifferentiated types in terms of lethal potential. Seventy-five per cent of these cancers are technically resectable from the surgical point of view, so that the incidence of early invasion of surrounding structures is not high. Nonetheless, almost half of the cases had distant metastases at the time when the diagnosis was first established, showing that this tumor differs from the papillary lesions in that it cannot be considered to be surgically "curable" to as great a degree.

The fact that almost two thirds of the patients had pre-existing goiters for more than three years is particularly significant and suggests that this group of carcinomas in particular may well arise in diseased thyroid glands. The possibility that malignancy had existed in a leisurely and localized form for many years cannot be overlooked but it seemed more likely from the individual histories that most of these cases had had benign thyroid disease for many years before malignant change occurred.

It has been the opinion of the members of the Thyroid Clinic of the Massachusetts General Hospital for many years that there are probably two different types of so-called adenocarcinoma of the thyroid. In this series of cases we have attempted to evaluate this clinical impression and have divided the follicular carcinomas into two groups on the basis of microscopic criteria. One group consists of those cases which showed little if any evidence of malignancy on microscopic examination and had not broken

through the surrounding capsule of the tumor; in fact in many of them the only evidence of malignancy was either the presence of invasion into blood vessels or the presence of distant metastases. In the second group, which has been called in Table 1 the follicular adenocarcinomas, there was distinct microscopic evidence of malignancy and evidence of local invasion well beyond the confines of any surrounding capsule. It has been interesting to see if there was any clinical distinction between these two histologic classifications. In the group of so-called localized carcinomas, only 3 patients died in less than two years after the diagnosis was established at this hospital. When these 3 were considered more closely it was apparent from their histories that the disease had existed for a much longer period of time; in 1 patient a diagnosis of cancer had been made at thyroidectomy at another hospital four years before her initial admission to the Massachusetts General Hospital, and in a second patient thyroid tissue had been found microscopically in a metastatic lesion in the vertebral column five years before he was first seen at this Clinic. Therefore out of this entire group there was only 1 patient who died less than two years after the diagnosis of thyroid cancer was first established. This presents a distinctly different clinical picture from that in the 26 patients with follicular adenocarcinoma, of whom 8 died in less than a year after the diagnosis was first established. Thus a good correlation existed between the microscopic criteria and the clinical course of the cases in these two groups. This division of the follicular carcinomas into two separate biologic entities is further substantiated by the appearance of the graphic representation of the cumulative survival rate of the total group of follicular carcinomas (Fig. 2). The striking biphasic quality has already been noted. No such biphasic quality was seen in the curves of undifferentiated and papillary cancers.

From this information it seems reasonable to say that the follicular carcinomas, taken as a group, usually arise in diseased thyroid glands, that the incidence is predominantly in the female, that the local resectability rate is high, but the incidence of early distant metastases is also high. The total picture is, therefore, quite different from that of the papillary type of cancer, and rational treatment should be employed, with these considerations in mind. In this type of cancer, age does not determine the type of therapeutic approach, as it might in the papillary group. All patients in this group, however, should have at least a total thyroidectomy at the time of the initial exploration. There is a relatively low incidence of regional node metastases and, therefore, radical neck dissection should be considered only if demonstrable lymph node metastases exist. The high incidence of distant metastases makes it apparent that one cannot rely on surgical methods alone to control the disease.

In this particular type of thyroid cancer the rationale of thyroidectomy

is twofold: 1) the eradication of the primary focus, and 2) ablation of functioning thyroid tissue in order that radiation therapy with I^{131} may be employed to control the distant metastases. There was considerable hope that when I^{131} became available, metastases from this type of follicular carcinoma would take up a high proportion of an administered dose of the isotope and thereby induce a high radiation potential in the metastatic lesion. In some cases treatment with I^{131} after removal of the primary tumor has been remarkably effective. Nonetheless, it would be fair to say that the initial optimism has not been borne out in a long-term survey of these cases. Of the 14 cases of metastatic thyroid cancer treated with I^{131} in this Clinic, 12 were classified as follicular carcinomas microscopically. The results of therapy are shown in Table 6. Six patients in this group were reported to show clinical improvement; but this interpretation was primarily subjective and only 1 of the patients with metastatic disease from the follicular carcinoma showed improvement by x-ray examination. Five of the 12 patients died of their disease and 1 was lost to follow-up. The other 6 patients have been living with evidence of disease for two years or more. One might say that this was evidence in itself that I^{131} had been effective in controlling the growth of the metastatic lesions, and this statement may well be true; but it is important to realize that the natural history of these metastases from follicular carcinoma is one of a relatively leisurely rate of growth, and there are several patients in this series, with untreated metastases who survived many years. Without more objective evidence of the effect of I^{131} on metastatic cancer of the thyroid, all that can be said is that results in this series of 14 cases are inconclusive. In 1 case already mentioned of metastatic pulmonary lesions from a primary papillary cancer of the thyroid, both clinical and x-ray improvement was rapid and dramatic. It is the impression of the members of this Clinic that 6 cases of follicular carcinoma were benefited by the use of I^{131}, but without more objective evidence this can be classified only as a clinical impression and valued as such. After total thyroidectomy, thiouracil drugs were employed in 6 cases in order to improve the uptake of I^{131} by the metastatic lesion. Apparently this was effective in at least 4 of these cases, if the change in total iodine uptake can be accepted as an index of the effect of thiouracil.

In summary, therefore, one can state that follicular cancer of the thyroid probably consists of two separate biologic entities. One type has characteristics of early invasion of surrounding structures and the patient has a relatively short duration of life if the disease cannot be surgically eradicated in its early stages. The other type is benign from the point of view of its local invasiveness, but early in its course shows distant metastases which may be ultimately lethal over a period of many years. Regardless of the histologic type of the tumor, the approach should be initially an attempt

TABLE 6. THE TOTAL NUMBER OF CASES OF THYROID CANCER TREATED WITH I^{131} AT THE MASSACHUSETTS GENERAL HOSPITAL (1931–1951) ANALYZED AS TO TYPE OF CANCER, LOCATION OF METASTASES, IMPROVEMENT BY CLINICAL AND ROENTGENOLOGIC CRITERIA, ADJUNCTIVE THERAPY DESIGNED TO INCREASE THE IODINE UPTAKE OF THE METASTATIC LESION, AND CLINICAL STATUS OF THE PATIENT AS OF JANUARY 1954

Case	Type of cancer	Metastases	Amount of I^{131} therapy (millicuries)	Improvement		Adjunctive therapy		Status of patient
				Clinical	X-ray	Total thyroidectomy	Thiouracil	
H.G.	Papillary	Axilla Lungs Spine	40	None	None	No	No	Dead—3 mos.
T.I.	Follicular	Skull	260	None	None	Yes	No	Dead—7 yrs.
J.B.	Follicular	Spine	1,100	3+	None	Yes	Yes	Living—8 yrs. 4 mos.
M.R.	Follicular	Liver	88	None	None	No	No	Dead—4 mos.
M.M.	Follicular	Spine Shoulder Pelvis	2,000	2+	None	Yes	Yes	Dead—5 yrs. 5 mos.
L.A.	Follicular	Spine Pelvis Skull	150	None	None	Yes	No	Dead—2 yrs. 2 mos.
C.D.	Follicular	Lung	130	None	None	No	No	Living—4 yrs. 3 mos.
M.S.	Follicular	Pelvis Sternum	1,000	2+	None	Yes	Yes	Living—4 yrs.
E.N.	Follicular	Spine Skull	35	None	None	Yes	Yes	Living—3 yrs.
L.V.	Follicular	Sacrum	150	1+	None	Yes	Yes	Lost to follow-up
M.P.	Follicular	Spine Skull Ribs	360	None	1+	No	No	Dead—6 yrs.
M.J.	Follicular	Hips Pelvis	300	1+	None	Yes	No	Living—2 yrs. 5 mos.
A.M.	Follicular	Hip	450	1+	None	Yes	Yes	Living—2 yrs.
L.D.	Papillary	Lungs	300	4+	4+	Yes	No	Living—2 yrs.

to cure the disease surgically by total thyroidectomy, with radical neck dissection only in the cases in which there are demonstrable lymph node metastases. Further therapy should depend upon the presence of demonstrable distant metastases. If these exist, the total ablation of normal thyroid function is important, since at present the only hope of control of the disease is the administration of I^{131} after a period of thiouracil therapy to induce a greater uptake by the metastatic lesion. It should be mentioned

briefly that some of these metastatic lesions have been surgically resectable. This is something to be considered in every case, since the presence of one or two metastases in this type of cancer does not necessarily mean widespread invasion of the entire organism.

UNDIFFERENTIATED CARCINOMA

In the past, many terms have been applied to various subdivisions of this group of cancers, *e.g.*, carcinoma simplex, round-cell carcinoma or anaplastic carcinoma. The common denominator of this group is that none shows any microscopic evidence of attempts to reproduce distinguishable thyroid structure. All of them appear to have a highly malignant potential and it seems reasonable to consider them all under the heading of undifferentiated carcinoma.

Microscopically there are two different types: one is composed of highly anaplastic giant cells often resembling sarcoma, and the other of small cells growing in either a compact or a diffuse arrangement. This subdivision is strictly morphologic, however, since there are no apparent distinguishing biologic characteristics.

From the data presented in Tables 1 and 2 and in Figures 2 and 3, it is apparent that these undifferentiated cancers occur only rarely before middle age, that the preponderance in the female is less striking than it is in the differentiated tumors, and that the mortality from the disease is high.

These tumors grow rapidly and invade surrounding structures so early that only 27 per cent of the total group of 45 cases were surgically resectable at the initial admission. Nonetheless, of the 12 patients whose tumors were considered resectable, 5 are living and well more than four years after operation. Therefore, although the over-all prognosis of these tumors is poor and 70 per cent of the patients died in less than a year after the diagnosis was made, the situation is not inevitably hopeless and a wide resection of an operable tumor offers some chance of salvage. In most cases, however, all the surgeon can accomplish is to free the trachea from the garrot of tumor tissue by resecting the isthmus. External radiation has been employed frequently but there was no evidence in this series that any palliation was achieved.

SUMMARY AND CONCLUSIONS

1. In the twenty years from 1931 to 1951, 190 patients with malignant disease of the thyroid gland were admitted to the Massachusetts General Hospital.

2. These cancers have been classified according to a method described by Warren and Meissner, which utilizes accurate terminology and takes

into consideration both the microscopic appearance and the biologic characteristics of the tumors.

3. Cumulative survival rates of the three main types of thyroid cancer (papillary, follicular and undifferentiated) have been calculated according to standard "life table" methods, and survival curves have been plotted. In brief, these survival rates are:

Cumulative survival to	*5 years*	*10 years*	*20 years*
Papillary	73%	60%	45%
Follicular	71%	48%	24%
Undifferentiated	17%	17%	17%

4. The sex and age incidences, the surgical resectability, the mortality from the disease, the incidence of regional and distant metastases, the incidence of pre-existing goiter and the five-year survival rates have been reported for the three main types of thyroid cancer.

5. The results of the treatment of thyroid cancer with I^{131} at the Massachusetts General Hospital have been tabulated.

6. From this information an attempt has been made to describe the biologic characteristics of the different types of thyroid cancer and to outline rational therapeutic approaches based on these characteristics.

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ANAPLASTIC CARCINOMA OF THE THYROID: EVALUATION OF POSTOPERATIVE RESULTS*

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IT IS well known that there is a marked difference in the rate of growth and clinical behavior of the various histologic types of thyroid carcinoma. The largest histologic group, namely papillary carcinomas, consists of slowly growing neoplasms whose natural history is now well understood. The role of the surgeon in the treatment of this form of carcinoma is well established. Extensive local surgical procedures may be combined with dissection of cervical lymph nodes, or even with radical dissection of mediastinal lymph nodes.

Additional histologic types of thyroid carcinoma, more malignant than the papillary form but of relatively slow growth, include the more or less circumscribed or encapsulated carcinoma variously called "malignant adenoma" or follicular and alveolar carcinoma. In this group, metastasis may occur by lymphatics to regional nodes or by the blood stream, particularly to bone. Hürthle-cell carcinomas, frequently encapsulated, make up a fairly well recognized histologic group, as do solid adenocarcinomas. All these have been excluded from this study.

BACKGROUND INFORMATION

The more modern literature has not contributed greatly to the special study of the anaplastic type of cancer. Most of the emphasis has been placed upon the incidence of carcinoma in a nodular goiter (1–4). Much of the earlier authoritative basis for the classification of thyroid cancer was presented by Graham (5) and also by Broders (6). Complete awareness of these different ideas formed the basis for discussion of the treatment of thyroid cancer by Pemberton (7), but there again the record for treatment

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of the anaplastic form was not good. Ten years after Pemberton's report Black (8) covered a similar series (also from the Mayo Clinic), indicating trends and a definite change in incidence. In 1951 Beahrs and Judd (9) touched briefly on the anaplastic form, without emphasis on surgical treatment except to admit that the 5-year survival rate was extremely low. Later that year Beahrs, Pemberton and Black (1) reported upon a striking trend, in that the incidence of so-called malignant adenoma was far lower than previously reported. A somewhat similar reduction was apparent for the anaplastic type, whereas the incidence of the papillary form had risen abruptly.

The present paper is concerned with the most rapidly growing, anaplastic cancers of the thyroid, a group which has long been associated with an extremely poor prognosis. The limited surgical treatment that is usually possible and the over-all poor results have combined to foster a pessimistic view on the part of the surgeon with regard to this group. We have reviewed our records in an effort to determine whether the treatment of this type of carcinoma might be improved.

PRESENT STUDY

The histologic sections of thyroid carcinomas seen over the 25-year period 1928 through 1952 were reviewed. From these were selected all that were characteristic of anaplastic thyroid carcinoma. This histologic grouping includes all cancers made up of various mixtures of spindle and giant cells, some of which strongly resemble sarcomas, and also large-cell and

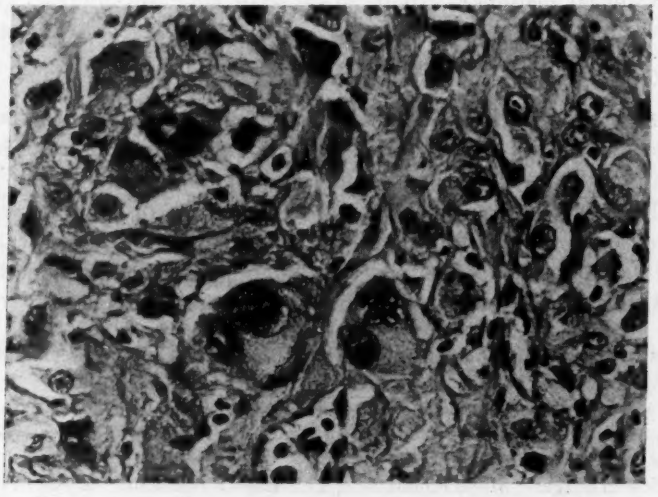

FIG. 1. Large-cell carcinoma (hematoxylin and eosin; ×400).

small-cell anaplastic carcinomas. In all varieties the tumors were highly infiltrative and the histologic pattern structureless. There were frequent mitotic figures and marked nuclear anaplasia.

In the group of small-cell anaplastic carcinomas are included all small-cell malignant lesions believed to be primary in the thyroid gland. As is true of small-cell malignant tumors at other sites, notably the stomach, there may be difficulty in distinguishing reticulum-cell and lymphosarcoma

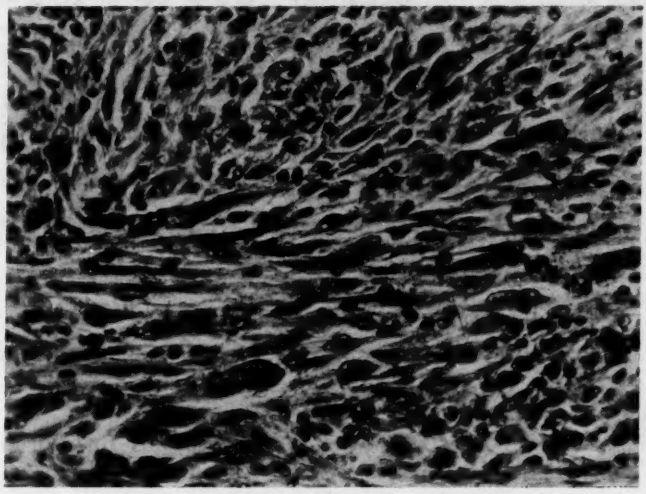

FIG. 2. Spindle-cell form of large-cell carcinoma (hematoxylin and eosin; ×400).

from small-cell carcinoma. In the present study no attempt has been made to exclude reticulum-cell or lymphosarcoma. A more detailed study of this aspect of the problem is in progress.

In all, 83 cases were available for study. In 58 of these cases the lesions were spindle and "giant-cell" or large-cell anaplastic carcinomas (Figs. 1 and 2). In the other 25 cases they were classified as small-cell carcinomas (Fig. 3). The average age of the patients was 55.7 years, with a range from 15 to 83 years.

METHOD OF TREATMENT

The series was separated into groups according to the method of treatment employed, regardless of cell type of the lesion. The results of this portion of the study appear in Table 1. It is to be noted that most of the patients received radiation therapy in some form. Perhaps the most favored method was external x-ray therapy administered as soon postoperatively as wound healing would permit. However, many other forms or combina-

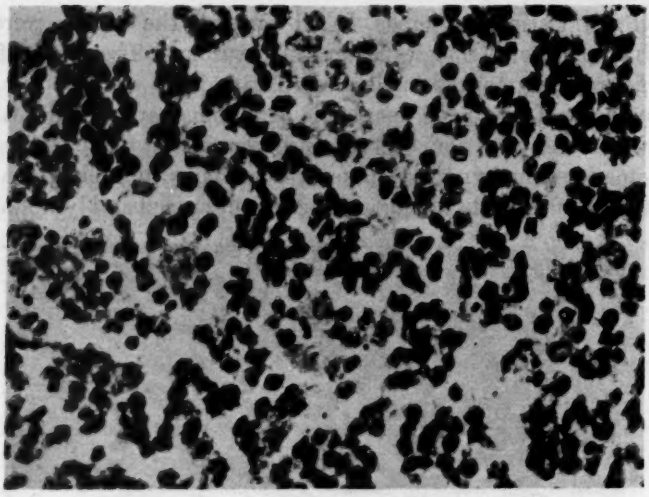

FIG. 3. Small-cell carcinoma (hematoxylin and eosin; ×425).

tions of radiation treatment were tried, so that results of statistical significance are not evident at present. The several methods will be discussed subsequently.

Although Table 1 does not reveal it, tracheotomy formed an integral part of many of the surgical procedures. A significant number of the patients were admitted with unilateral vocal-cord paralysis, largely due to malignant invasion of the recurrent laryngeal nerve, but in several instances following previous operation upon the gland. Tracheotomy usually was a planned part of the operation, not only to insure a good airway post-

TABLE 1. ANAPLASTIC CARCINOMA OF THE THYROID: TREATMENT

Treatment	No. of cases
Biopsy only	10
Biopsy plus radiation	35
Resection of one lobe plus radiation	14
Bilateral resection plus radiation	8
Unilateral lobectomy, removal of isthmus and subtotal removal of opposite lobe plus radiation	5
Unilateral lobectomy plus radiation	7
Total thyroidectomy plus radiation	4
Total	83

operatively but also to render possible an intensive course of radiation therapy without fear of tracheal obstruction on the basis of severe reaction to treatment.

RESULTS OF TREATMENT

It was evident at the completion of our study that there was a great difference between survival figures for the various cell types. In general, those patients with predominantly spindle-cell carcinoma had an average survival period of only four months, representing one of the most malignant forms of disease encountered anywhere in the body. In sharp contrast, the small-cell form suggested a far less dire circumstance, as many of the cases with a better prognosis fell into that group.

The previous spirit of pessimism appears well founded when one refers to the information on survival in Table 2. However, it was consistently

TABLE 2. ANAPLASTIC CARCINOMA OF THE THYROID: SURVIVAL RATES BY TYPE OF TREATMENT

Treatment	Number of patients*	Lived 1 or more years after treatment		Number of patients*	Lived 3 or more years after treatment	
		Number	Survival rate, %		Number	Survival rate, %
Biopsy only	10	3	30.0	9	0	—
Biopsy plus radiation	35	13	37.1	32	2	6.3
Resection plus radiation	38	14	36.8	30	6	20.0
Total	83	30	36.1	71	8	11.3

* Inquiry as of January 1, 1954. All patients were traced and included in the 1-year group; included in the 3-year group are only those patients treated three or more years prior to the time of inquiry, that is, in 1950 or earlier.

true that the untreated patients fared less well than those with some treatment, and those who underwent more radical operations appeared to survive longest of all, as shown by the survival rates in Table 2. It is obvious that a large proportion of those who had only biopsy presented themselves in a rather hopeless condition and hence the comparison is not entirely fair.

It was thought important to determine if possible just where in the time scale the survivors were located. Of the 8 patients noted in Table 2 to have lived three or more years after treatment, 2 received radiation only and 6 underwent resection plus radiation. One patient who received only radium therapy lived four years, and another who received a combination of radium and x-ray therapy but who did not undergo a radical operation lived

five years. Of passing interest is the fact that the 1 patient who was living after seven years had a small-cell carcinoma. He was 79 years old at the time of total right lobectomy with complete removal of the isthmus and resection of the left lobe. The operation was followed by radium and deep x-ray therapy. An additional 3 patients were alive five years after operation, and the remaining 2 patients lived three years.

The brief for surgical treatment may be a very weak one indeed but it is interesting that of those patients surviving three years or more, all underwent a more extensive procedure than mere biopsy.

COMMENT

One is tempted to draw a bizarre conclusion when one notes that in certain cases biopsy followed by radiation treatment appeared to give better results than more radical surgical procedures. However, the series at hand does not permit the drawing of definite conclusions; close scrutiny leads to the assumption that the findings would be more apparent than real. It is evident that throughout the series the surgeons were faced with extreme technical problems. Anaplastic carcinoma commonly presents an almost hopeless situation, in sharp contrast to the low-grade papillary lesion which is easily encompassed and the secondary deposits of which may be removed easily, even at a late date. The morbidity study in this series revealed considerable differences, and from the records of some of the cases of anaplastic cancer the impression is derived that the surgeon wished he had stopped sooner, since rather distressing complications attended occasional radical attempts. However, the trend in the series as the years progressed was toward a more aggressive surgical attack. This was obviously predicated upon the tremendous advances which have been made in the fields of surgical adjuncts rather than upon any new triumph of surgical technic. The role of radical dissection of the neck is obviously very minor here, because of the nature of the cancer. In many cases the surgeons were pleased to be able to establish the diagnosis, to clear the trachea, and occasionally to perform a proper tracheotomy in order to make subsequent intensive radiation therapy safe.

The role of radiation therapy is impossible to assess in this series. Since most of the patients received some form of radiation regardless of the type of surgical treatment, no valid figures are forthcoming. The external application of x-rays often supplemented surface "packs" of radium. In earlier years, large, stiff, rubber drains were commonly placed in the cancer bed and, through these, radium applicators were soon inserted. In a few cases interstitial therapy (in the form of radon seeds) was applied. At present all patients suspected of having thyroid cancer receive preoperative doses of radioiodine. The data obtained in the laboratory preoperatively (Geiger

counts and urinary excretion) are combined with the information derived from the autoradiogram of the surgical specimen. To date, the results of treatment of this form of cancer with radioiodine have not been encouraging.

SUMMARY AND CONCLUSIONS

1. Anaplastic carcinoma of the thyroid gland remains a lesion that entails a very poor prognosis.

2. Surgical efforts can scarcely be listed as curative or even very effective. The surgeon can establish the diagnosis, perform tracheotomy as indicated to facilitate intensive radiation therapy, and very occasionally remove malignant tissue in a fairly complete fashion.

3. The cell types outlined here appear to have a definite bearing in prediction of the usual clinical behavior.

4. Although past experience has demonstrated a relatively minor role on the part of the surgeon, the trend at present is toward a more aggressive attack, owing entirely to the great improvements in surgical adjuncts.

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INVASIVE PAPILLARY CANCER OF THE THYROID*

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SEVERAL pathologists—friends of ours, we hope—have noted the misleading title of this paper. They quite properly point out that papillary cancers of the thyroid are usually unencapsulated and that blood vessel invasion is common and may on occasion be demonstrated in lesions only a few millimeters in diameter.

It is well known that many papillary cancers are small, are embedded within the gland substance, and fail to show gross evidence of either infiltration of neighboring structures or metastasis to the regional nodes. The clinical course of most of these tumors is so sluggish and prolonged as to give rise to misleading concepts concerning the clinical course of papillary cancers as a group. It should be stressed that such physical characteristics do not necessarily influence the ability of these tumors to metastasize to regional nodes or, for that matter, to distant sites. In fact such metastases are often the initial and only complaint of the patient for years prior to the discovery of the primary tumor and, hence, the formerly widespread misconception of the so-called "aberrant thyroid" tumors.

Other papillary thyroid cancers, in no wise histologically distinguishable from others in the group, are those which are aggressive from their clinical outset; and it is this group with which we are presently concerned. These lesions have in our experience been characterized by invasion of neighboring structures, such as the ribbon muscles, the trachea, oesophagus and, on occasion, the carotid sheath. Extension into the mediastinum is common and metastases to lymph nodes are noted in one or both sides of the neck. Although the clinical course of this group of cancers may be prolonged, it is characterized by failure of control of the disease and ultimate death of the patient.

MATERIAL

This report is concerned with the clinical features observed in 63 patients suffering from papillary cancer of the thyroid observed during the

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past twenty years at Memorial Hospital, in whom failure to control the tumor has been proved or can be predicted. Forty-three of these patients are dead and 20 are living with known or suspected residual disease. All tumors were classified as papillary on the basis of adequate surgical material. All conformed to the usual criteria used to designate the papillary group of tumors, though as would be expected, some showed varying proportions of follicular or alveolar components. From the histologic point of view, these tumors were all notably low-grade.

In a previous report from this clinic (1), it was indicated that approximately 20 per cent of our papillary thyroid cancer patients with long-term follow-up were dead of their disease under conventional forms of therapy. This obviously does not represent the true incidence of the more aggressive tumors, since no one of us has lived long enough to follow a large group of such thyroid cancer patients throughout their entire clinical course. It seems highly likely that some of the patients in this series, although their disease is now quiescent, will ultimately die of their tumors. This phenomenon of delayed aggressive characteristics of the so-called low-grade papillary thyroid cancer seems to have been inadequately appreciated by some observers. It suggests that observations based on short follow-up periods are of questionable value.

Some surgeons believe that an aggressive surgical approach to the treatment of the papillary group of thyroid tumors is unnecessarily radical. It has been suggested that the pessimistic attitude often expressed by Memorial Hospital surgeons concerning the clinical course of these tumors was due to the nature of the material examined. It is true that we see many of the advanced, the recurrent and the problem cases. Many of them represent the end-results of treatment by surgeons now dead, or living in blissful ignorance of the late course of the disease. Not all of our material falls into this category, however, and it should be noted that in this report primary and previously treated aggressive papillary tumors occurred in almost the same proportions (Table 1).

PROGNOSIS OF PAPILLARY TUMORS

Incomplete surgery. It may be said with little fear of contradiction that the failure of the initial surgeon to remove all of the local disease is a vital factor in at least the local spread of papillary thyroid cancer. Recognizing the possibilities of clinical error in the preoperative diagnosis, and the occasional shortcomings of frozen-section diagnosis, we have for years endeavored to minimize the possibility of incomplete removal of the primary tumor by advising and practicing complete thyroid lobectomy for all solitary thyroid nodules. Recent studies (2, 3) suggest that such advice is equally applicable to the thyroid lobe containing multiple nodules. Should

TABLE 1. DISTRIBUTION OF 63 PATIENTS WITH INVASIVE PAPILLARY THYROID CANCER

	Deaths	Patients living with disease
Primary thyroid cancer	22	10
Recurrent thyroid cancer	21	10
Totals	43	20

the lesion prove cancerous, neck dissection is in order. We are convinced of the wisdom of avoiding scarring of the lateral aspects of the neck by local excision of nodes, unless one is prepared to perform neck dissection. Experience in this clinic includes a large number of secondarily treated papillary thyroid cancers. Such experience clearly indicates that once the tissue planes of the neck are scarred by one or more surgical maneuvers, adequate neck dissection at a later date becomes impossible.

It should be pointed out, however, that it is not always possible to excise the primary lesion completely in papillary thyroid cancer. It has been our unfortunate experience to perform the initial operation on several patients with papillary tumors in whom the disease was nonresectable due to extensive invasion of vital structures. Although the excision of such structures may on occasion be justified, the decision to do so should be balanced with the likelihood of ridding the patient of his disease.

Age of the patient. In this series approximately 40 per cent of the patients were less than 40 years of age at the time of diagnosis. The age at onset in any patient with cancer is difficult to determine and this is particularly true for the papillary tumors, in which thyroid enlargement or nodes in the neck may exist for years or even decades prior to diagnosis. It therefore seems likely that in numerous patients in the older age groups papillary

TABLE 2. PROBABLE AGE OF PATIENT AT ONSET OF THYROID CANCER

Age of patient (yrs.)	Deaths	Patients living with disease
Under 10	1	2
10–19	3	5
10–29	4	3
30–39	6	2
40–49	12	2
50–59	8	1
60 and over	9	2
Not stated	0	3

cancer developed before the age of 40 years. We have been able to determine fairly accurately the apparent age at onset of the neoplasm in some of our patients, since several of them were children. A previous report from this hospital (4) indicated that only 50 per cent of thyroid tumors in children are of the papillary type. To date, the clinical course in children has not been outstandingly more favorable than that in older age groups. As the follow-up of these patients continues, it becomes evident that age groupings of patients with papillary tumors is of limited significance in determining the ultimate prognosis (Table 2). Efforts to give this factor precedence over histologic variations of tumor seems to be over-simplifying the problem (5).

CAUSE OF DEATH

The ultimate cause of death of any patient with cancer may be difficult to determine, and papillary cancers of the thyroid prove no exception. We have listed (Table 3) the apparent cause of death in 43 patients. It is significant that generalized disease and lung metastasis played such an important role in these deaths.

The actual extent of the disease at the time of death (Table 4), as con-

TABLE 3. CAUSE OF DEATH IN 43 PATIENTS WITH THYROID CANCER

Generalized disease		11
Lung metastasis		13
Local disease		9
Mediastinal disease only		3
Other:		
Postoperative	3	
Complication of irradiation	2	
Suicide, with disease	1	
Old age, with disease	1	

firmed by clinical, radiographic and autopsy findings, confirms the unpredictable clinical course of the tumors. As would be expected, persistent local disease with resulting asphyxia in some cases was exceedingly common. The failure to record a higher incidence of mediastinal involvement is, we believe, due to the low percentage of autopsies obtained, as most of these patients died at home.

CONCLUSIONS

Papillary cancer of the thyroid can be, and often is a fatal disease, even though the clinical course is prolonged. Some of these tumors are aggressive from the time of clinical onset and may prove technically inoperable at the

TABLE 4. SPREAD OF DISEASE AT TIME OF DEATH

	No. of times recorded
Local disease	30
Lung	18
Mediastinum	4
Bone	
Spine and pelvis	7
Skull	2
Tonsil	1
Eye	2
Brain	3
Abdomen	2
Pleura	1

time of initial surgery. Others may not exhibit their aggressive characteristics for many years. Further study of the clinical course is indicated before any significance can be attributed to such data as the age of the patient or histologic variations of the tumor. Any dogmatic statements concerning this disease, including those in this report, are liable to be refuted in time.

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EXPERIMENTAL PRODUCTION OF THYROID TUMORS BY ALTERNATING HYPERPLASIA AND INVOLUTION*

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THE genesis of the thyroid nodule and its relation, if any, to tumors of the thyroid gland continues to be a challenging aspect of the thyroid problem. Perhaps the most widely accepted explanation for the origin of nodules in the thyroid gland is the concept that they are the result of repeated cycles of hyperplasia and involution. Certainly, most of the statistical data concerning such aspects as the frequency, distribution or age incidence are in accord with this view. Nevertheless, there has been no actual proof of this hypothesis and, to the best of our knowledge, no one has experimentally produced a nodular goiter by making the gland go through successive cycles of hyperplasia and involution a sufficiently large number of times. Many years ago when goiter was an important and prevalent condition, one of us (L. Z.) attempted this experiment in the dog; but at that time (before the goitrogens had been discovered) reliable methods of producing thyroid hyperplasia were not available. Moreover, the laboratories in which the experiments were carried out used iodine very freely for surgical preparation of the skin, and there was probably enough iodine in the atmosphere to have exerted a very considerable antigoitrogenic effect.

When it was demonstrated that through the use of goitrogenous substances it is possible to produce hyperplasia of the thyroid gland at will, and that long-continued stimulation of the thyroid gland by continued feeding with propylthiouracil and other goitrogens results in the formation of thyroid tumors, we became interested in taking up this old problem.

MATERIAL AND METHODS

Young adult white rats were maintained alternately on propylthiouracil to produce hyperplasia, and on potassium iodide to involute the thyroid

* Presented at the Annual Meeting of the American Goiter Association, Boston, Mass., April 29–May 1, 1954.

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gland. The propylthiouracil was administered in the drinking water in a concentration of 0.1 per cent, and the animals were allowed to drink as much as they chose. With this dosage, pilot experiments indicated that a considerable degree of hyperplasia could be produced within two weeks. The involution was rapidly accomplished by substituting potassium iodide in concentrations of 0.01 per cent in the drinking water; and pilot experiments showed adequate involution. For controls, we had a similar series of rats that were maintained on continuous propylthiouracil feedings alone, and a small number that were kept on continuous potassium iodide feedings.

It was our plan to continue these experiments for a minimal period of two years, but unfortunately we were compelled to terminate them shortly before the first year was completed. We had acquired new laboratory facilities and were not permitted to bring the old cages and animals into the new quarters. Very reluctantly then, the animals were sacrificed. This apparent misfortune proved to be quite the opposite for us because, although the production of thyroid nodules had not progressed to a definitive point, we were surprised to find tumors in the thyroid glands of our experimental animals in a considerably higher incidence than in the controls undergoing continuous stimulation with propylthiouracil.

A certain number of the rats had been sacrificed at varying intervals and their thyroid glands removed for section. These, and the animals that died of intercurrent causes were used for study of the changes in the thyroid gland. The thyroids of these animals and of those sacrificed at the termination of the experiment were removed *en bloc* with the trachea and esophagus, and fixed for histologic study. At least eight sections were taken from each specimen.

RESULTS

Only 44 animals of the original 100 survived to the end of the experiment —29 of the propylthiouracil-iodine group, and 15 controls fed with propylthiouracil only. The group given alternate thiouracil and iodine showed a higher incidence of thyroid tumors than the controls. The difference was statistically significant: 17 out of 29 rats in the first group had thyroid tumors (19 adenomas and 1 carcinoma) whereas, among the 15 controls, only 4 had tumors, all single and benign (Table 1).

TABLE 1. ADENOMATA IN SURVIVING RATS

	No. of survivors at end of expt.	Rats with adenomata	Total no. of adenomata
Thiouracil and KI alternately	29	17	20
Thiouracil continuously	15	4	4

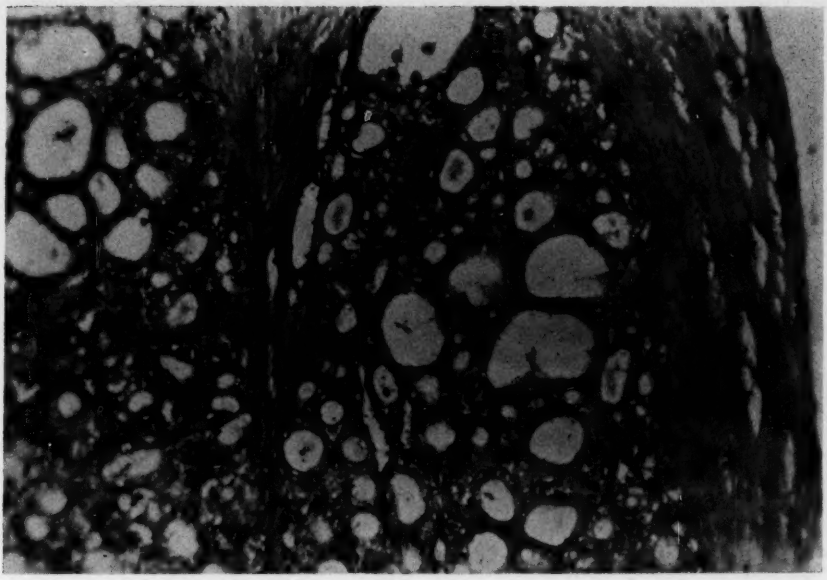

FIG. 1. Hyperplasia of thyroid during thiouracil treatment. ×120

The hyperplastic changes in the thyroid gland during propylthiouracil feeding and the subsequent involution during potassium iodide feeding are shown in Figures 1 and 2. In glands that had gone through the cycle a number of times, localized areas of hyperinvolution were seen (Fig. 2). These areas consisted of greatly dilated acini filled with colloid, and appeared to be early stages in the formation of involutional bodies or colloid nodules.

Three types of neoplastic change were encountered in the thyroid glands. The first of these resembled the so-called fetal adenoma. These tumors consisted of cords of cells and of small, elongated acini which contained little or no colloid (Fig. 3). The cells were tall columnar, with hyperchromatic nuclei. The adjacent thyroid tissue was somewhat compressed, but no capsule had formed.

Whether these were benign tumors, or whether they represented localized areas of hyperinvolution (hyperplastic nodules), cannot yet be definitely stated. It is hoped that by following the evolution of these changes for a considerably longer period, we may be able to establish their identity.

The most frequently encountered neoplastic change was a benign adenoma of the "embryonal" type (Fig. 4). It consisted of closely packed polyhedral cells, with vesicular nuclei and abundant, granular eosinophilic cytoplasm. Serial sections showed most of these tumors to be solid, though occasional small acini were noted. The surrounding thyroid tissue was somewhat compressed, but there was no capsule.

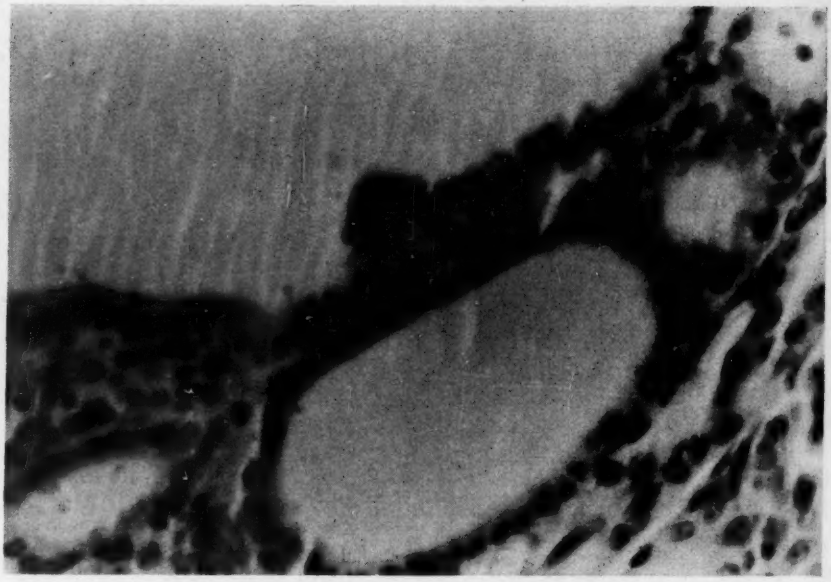

FIG. 2. Localized area of hyperinvolution in thyroid gland during alternate administration of thiouracil and potassium iodide. ×460.

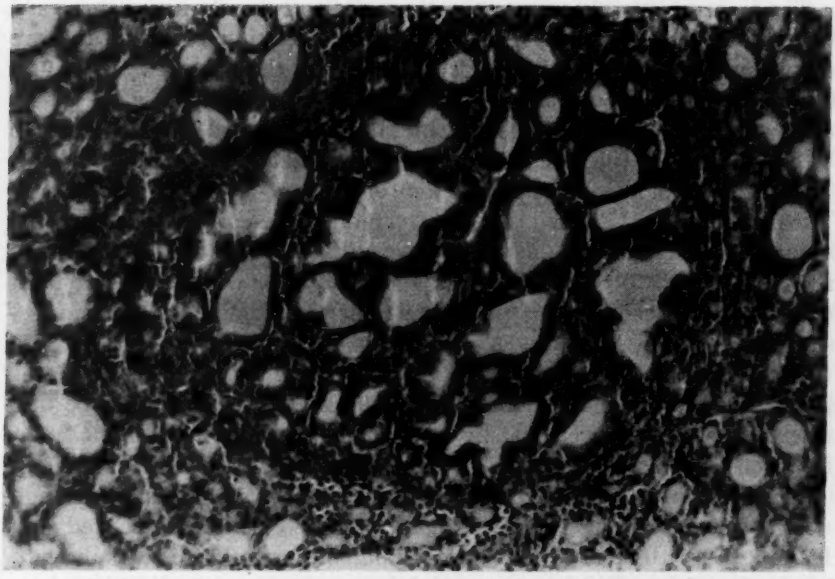

FIG. 3. Circumscribed zone of microfollicular hyperplasia resembling "fetal" type of adenoma. ×120.

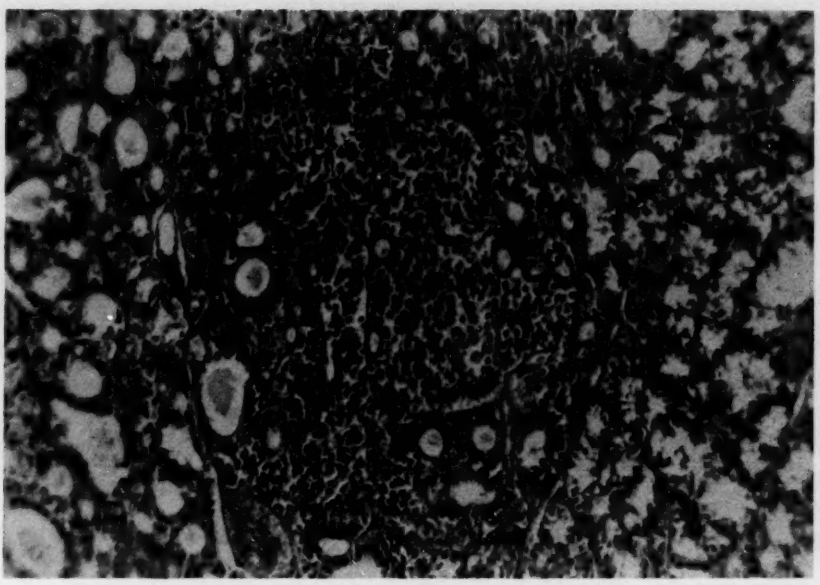

FIG. 4. Solid adenoma of the "embryonal" type. ×120.

The third type of tumor was found only once—in a rat treated with thiouracil and iodide alternately. This was a large lesion which almost completely replaced an entire thyroid lobe. It was cystic, with a large cavity almost entirely filled by papillary projections (Fig. 5). The surrounding thyroid tissue was compressed.

Histologically, the tumor was made up of several layers of hyperchromatic and pleomorphic cells with a few mitoses (Fig. 6). Invasion of blood vessels was demonstrated on serial sections. The tumor was considered to be a papillary adenocarcinoma.

DISCUSSION

This is in the nature of a preliminary report, and further studies are in progress. The feeding experiments are being repeated, and are already well under way. The period of observation will be extended to the limits of survival of the animals, and additional types of controls are being used.

One factor which may have a bearing on the described findings is the difference in the nutritional status of our experimental animals as contrasted with the controls. The control animals on continuous thiouracil feeding were, on the whole, poorly nourished and weighed less than did the experimental animals. It is known that undernutrition offers some protection against tumor formation. However, in the experimental animals, tu-

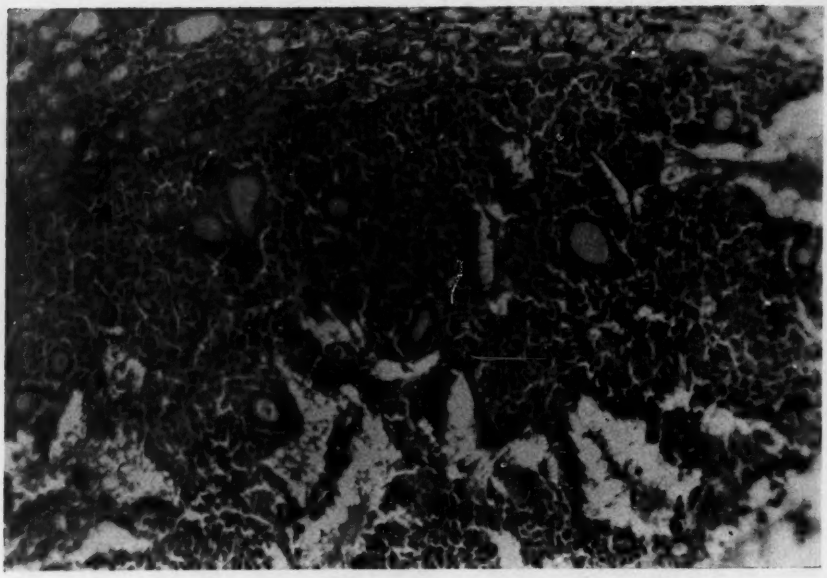

FIG. 5. Papillary adenocarcinoma. ×120.

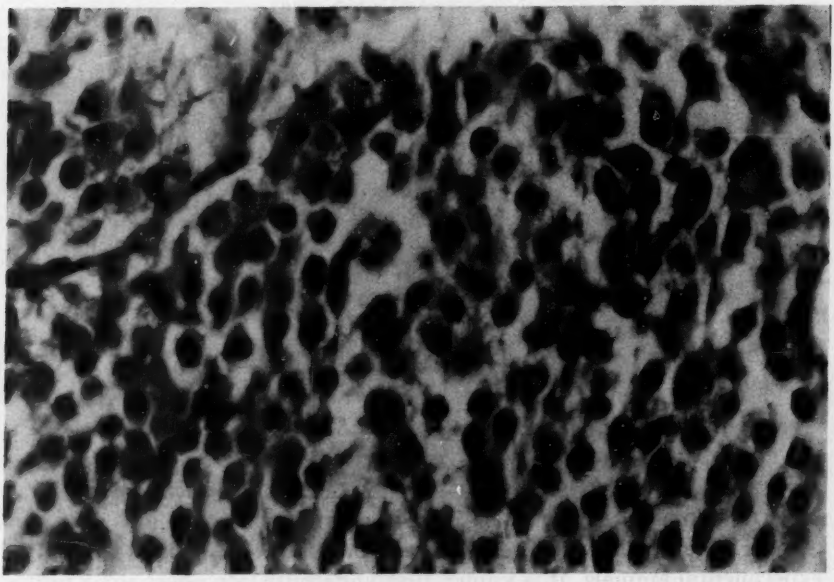

FIG. 6. High-power view of papillary adenocarcinoma. ×460.

mors were seen as often in the poorly nourished animals as in the better fed ones.

This mode of production of tumors is of interest because there is little, if any, contact of the epithelial structures with a carcinogen, unless propylthiouracil can be considered a carcinogen. In order to control this possibility, we are including a series of animals in our present studies in which hyperplasia is being produced by the administration of thyrotropic hormone. Should tumors result from this procedure, they will be due entirely to metabolic changes and not to contact between the cells and a carcinogenic agent.

SUMMARY

Although we have not solved our original problem, namely, the possibility of producing nodular goiter by alternating cycles of hyperplasia and involution of the thyroid gland, we have found that such alternation is much more effective in the production of neoplasms of the thyroid gland than is sustained stimulation. This may prove to be true of other experimental benign and malignant tumors. It is in keeping with the clinical observation that structures which undergo the most frequent and radical morphologic changes in response to fluctuations in physiologic activity are also often the ones that tend to exhibit both benign and malignant neoplasia.

METHOD FOR INCREASING THE ACCURACY OF THE RADIOIODINE UPTAKE AS A TEST FOR THYROID FUNCTION BY THE USE OF DESICCATED THYROID*†

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THE accumulation of radioiodine by the thyroid has become well established as one of the most sensitive and reliable tests of thyroid function. Nevertheless, there are some patients seen at most clinics in whom it is impossible to make an unequivocal diagnosis with this procedure. These usually fall into three groups: a) patients with many signs and symptoms of hyperthyroidism but with thyroidal radioiodine uptake within the normal range; b) patients with little or no clinical evidence of hyperthyroidism but with I^{131} accumulation above the normal range; c) patients with or without symptoms, who have an equivocal, "borderline" uptake ranging between the euthyroid and hyperthyroid levels. A fourth group of patients who are clinically euthyroid but have a subnormal uptake are not included in this consideration, since such a discrepancy is usually explained by saturation of the "iodine pool" of the body.

It has been found that the daily administration of physiologic amounts of desiccated thyroid to euthyroid subjects will result in a suppression of their thyroidal radioiodine metabolism to levels seen in myxedema (1). The present study was designed to extend the observations of the effect of exogenous thyroid to include patients with simple goiter and those with hyperthyroidism. It was found that patients with simple goiter had approximately the same degree of thyroid suppression induced by an equivalent amount of exogenous thyroid hormone as did euthyroid patients without goiter. Thyrotoxic patients, on the other hand, required much larger amounts of thyroid to produce appreciable depression of their thyroidal radioiodine metabolism. A technique is described, utilizing these results,

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which in our experience has proved to be helpful in differentiating euthyroid and hyperthyroid patients who present either an equivocal clinical picture or an equivocal thyroidal radioiodine accumulation.

MATERIALS AND METHODS

Patients from the Boston City Hospital, New England Center Hospital, and Massachusetts Memorial Hospitals of Boston and from District of Columbia General Hospital, Washington, D.C., were utilized for the study. Representative case histories are given in the Appendix. Most of the patients in Boston were white, most in Washington, colored. Only patients whose subsequent course and response to treatment satisfied our criteria for judging them to be undeniably either euthyroid or thyrotoxic are included in this report. It was necessary to exclude one patient because she stopped returning to the clinic before a definite diagnosis could be made. There were 28 patients with thyrotoxicosis and 55 euthyroid patients with goiters. Approximately 85 per cent of both groups were women. The youngest patient was 13, the oldest 72.

Radioiodine studies in Boston were performed as previously described (1,2). Both the "accumulation gradient," plotted as a percentage of the administered I^{131} against the square root of the time in minutes (2, 3), and the 24-hour uptake were studied in the majority of thyrotoxic patients; but since both values were found to be approximately equivalent, the accumulation gradient was later discarded. A 50-microcurie tracer dose was administered twenty-four hours before external thyroid counting with a shielded bismuth cathode gamma counter (Sylvania GG 306) at a distance of 55 cm. from the effective counting center. With repeated tracer studies, the residual radioactivity in the thyroid just before administering the next tracer dose was assumed to remain essentially unchanged during the next twenty-four hours. After correcting for decay, the residual count was subtracted from the total thyroidal radioactivity the next day to give the corrected 24-hour uptake.

Studies in Washington were similarly performed, except that a directional bismuth cathode gamma counter (Sylvania 322-DB) with a 15° aperture and without additional external shielding was used.

Following the initial uptake, the patients were given 180 mg. of U.S.P. desiccated thyroid (Armour), which they took daily for from one to two weeks. Radioiodine studies were repeated and the dosage schedule of thyroid increased for the next period. In almost all patients, the amount of thyroid given was increased by 180 mg. each one-week or two-week period until thyroidal accumulation of radioiodine was suppressed to, or near the 0 to 10 per cent level seen in myxedema, or until a total daily dose of 720 mg. had been given for at least one week. This was the maximum amount given to any patient.

Thorough clinical evaluation, including determination of the basal metabolic rate and serum protein-bound iodine level in some instances, was made at each visit.

All of the 55 euthyroid goitrous patients were given increasing doses of thyroid until their 24-hour I^{131} uptakes were less than 20 per cent, but further studies were not performed in the majority, once their uptakes had been suppressed below 10 per cent. Thus only 1 of these patients received more than 540 mg. of thyroid daily. If possible, thyrotoxic patients were continued until a dose of 720 mg. of thyroid was given daily, but 8 patients had to be dropped before completion of the study—6 because antithyroid therapy had inadvertently been instituted and 2 because of increasing subjective complaints.

Five additional thyrotoxic patients were studied by this technique, but received medication other than thyroid. Three were given iodinated casein (Protamone) and 2

were given potassium iodide in a daily dose containing the same amounts of iodine respectively as in 360 and 720 mg. of desiccated thyroid.

RESULTS

The changes produced in the thyroidal radioiodine accumulation by increasing doses of thyroid are plotted graphically in Figures 1 and 2. The goitrous euthyroid patients responded in a manner similar to the nongoitrous euthyroid subjects studied previously (1). Only 4 of the 55 patients had uptakes above 10 per cent while taking 360 mg. daily, and all had uptakes below 20 per cent when taking 540 mg. daily.

The ingestion of desiccated thyroid had a much less pronounced effect in the thyrotoxic subjects. In most patients there was no appreciable suppression of thyroidal radioiodine accumulation, even when a dose of 720 mg. was given daily. In some, however, there was a gradual suppression of thyroidal uptake with increasing doses of thyroid. The 24-hour uptake was never suppressed below 18 per cent in any patient and was suppressed below 20 per cent in only 1 patient, who at the time was taking 720 mg. daily and whose initial pretreatment uptake was 96 per cent.

In one 21-year-old thyrotoxic girl, the uptake fell from a pretreatment level of 68 per cent to 25 and 24 per cent respectively, while taking 180 and 360 mg. of thyroid daily. Further studies were prevented because of the institution of treatment with propylthiouracil by another physician at that time.

In the 4 thyrotoxic patients in whom the serum protein-bound iodine level and basal metabolic rate were determined at the same time as the

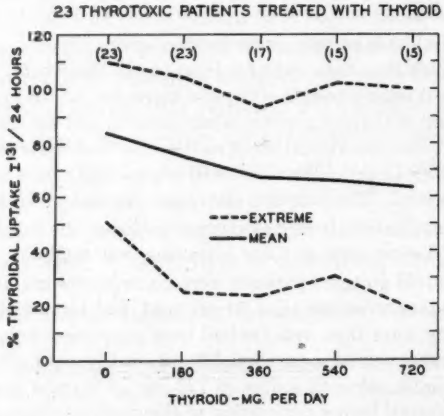

FIG. 1. Numbers in parentheses refer to number of patients treated with each dose of thyroid.

radioiodine uptake, it was found that the concentration of protein-bound iodine showed an increase over the pretreatment level during the first week of thyroid administration, then returned to the pretreatment level and remained there for the duration of the experimental period (Figs. 3 and 4).

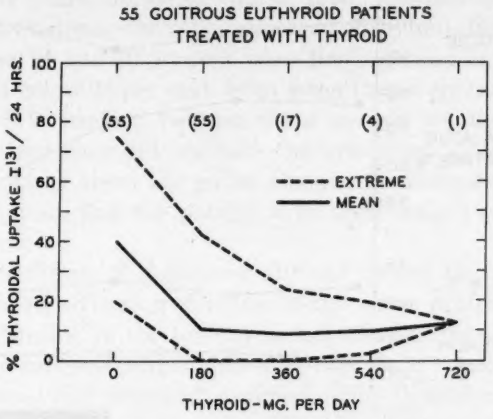

FIG. 2. Numbers in parentheses refer to number of patients treated with each dose of thyroid.

The basal metabolic rate was unaltered during the entire period of thyroid ingestion, as was the pulse rate. The body weight remained constant in all except 1 patient, who experienced a 12-pound weight gain during the month of thyroid administration (Fig. 4).

Most patients stated that they had benefited by the course of thyroid, but only in the patient with the 12-pound weight gain was there objective evidence of improvement. In 2 patients, as previously mentioned, it was felt advisable to discontinue thyroid because of increasing subjective complaints, but again there was no objective evidence of a change in the patient's clinical status.

Treatment with iodinated casein decreased the 24-hour uptake and serum protein-bound iodine value in all 3 patients, but not below euthyroid levels. In 1 of these patients the treatment apparently blocked at least a part of the organic binding of radioiodine. The I^{131} accumulation curve was typical of those seen in subjects given a blocking dose of propylthiouracil shortly before radioiodine administration (4) and some of the iodine could be discharged from the gland by thiocyanate administration. In 1 of the 2 subjects given potassium iodide the thyroidal radioiodine accumulation was decreased from 76 to 38 per cent; in the other there was no significant change from the pretreatment level.

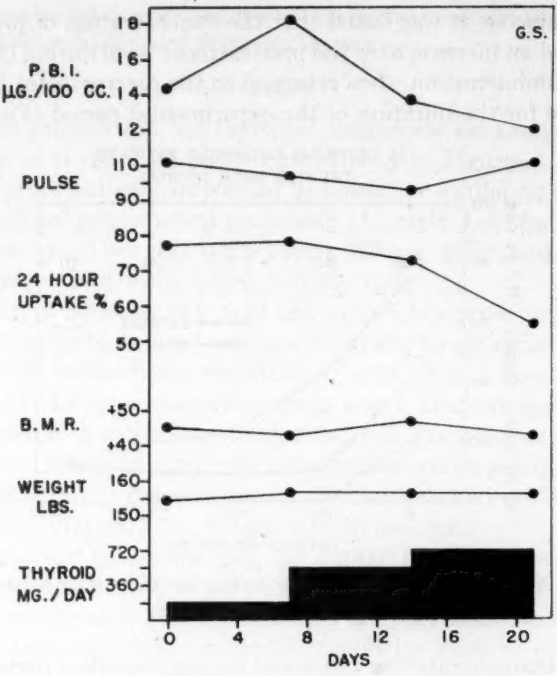

FIG. 3. Effects of increasing doses of thyroid for three weeks in a 30-year-old white male with recurrent hyperthyroidism of three years' duration.

DISCUSSION

These results show that there is a marked difference in the suppression of thyroid function produced by desiccated thyroid in thyrotoxic patients from that produced in goitrous euthyroid subjects. In all the euthyroid subjects, suppression of the 24-hour uptake was reduced to less than 20 per cent by the administration of 540 mg. or less of thyroid daily. In none of the thyrotoxic subjects was suppression below 24 per cent produced by the same level of thyroid ingestion. Werner has noted a similar difficulty in suppressing the uptake of thyrotoxic subjects with desiccated thyroid (5).

It thus appears that the administration of exogenous thyroid hormone may be a useful test in clarifying the status of patients who are clinically euthyroid but have a high or borderline accumulation of radioiodine, and those who have many symptoms of hyperthyroidism but have a normal or borderline uptake. None of the goitrous euthyroid subjects, but 8 of the thyrotoxic subjects in this study had uptakes between 50 and 75 per cent. Differentiation was easily made in all instances by means of the ease of

thyroidal suppression by exogenous thyroid. Prolonged subsequent study confirmed the diagnosis in each case.

Only 2 exceptions, not included in the present study, have so far been found. These were twin 60-year-old colored sisters, both of whom had large goiters of many years' duration. One of them also had classic signs and symptoms of myxedema; the other appeared euthyroid. Both had 24-hour uptakes between 60 and 70 per cent when first seen and in neither was the uptake reduced below 24 per cent, even when they were taking 720 mg. of thyroid daily. It is possible, because of the obvious mental retardation of both patients, that they did not take the prescribed amount of thyroid. However, in both of them the goiter completely disappeared while they were taking thyroid, and the patient with myxedema was returned to a euthyroid status.

Why administration of desiccated thyroid to the thyrotoxic patients should have caused no lasting elevation of the serum protein-bound iodine level or augmentation of the toxicity is not clear at present. Since both iodinated casein and potassium iodide were capable of lowering the protein-bound iodine level and thyroidal radioiodine accumulation, it is possible that the iodide released from the exogenous thyroid may have had the same

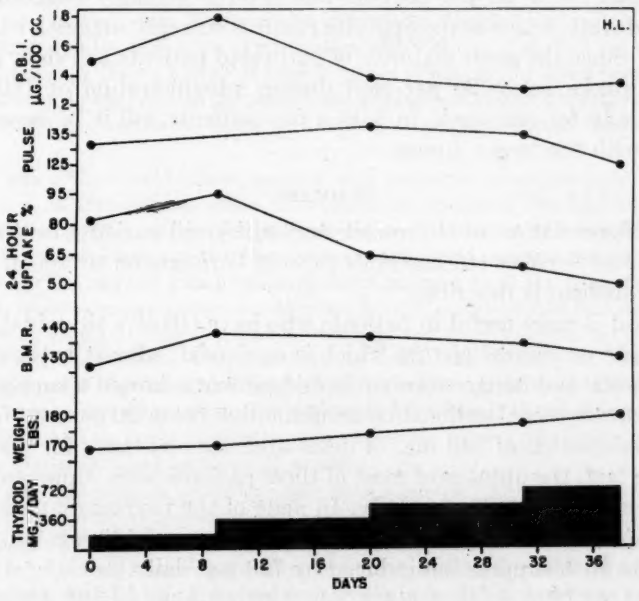

FIG. 4. Effects of increasing doses of thyroid for five and a half weeks in a 43-year-old white male with hyperthyroidism of one year's duration.

effect. The administered thyroid hormone would thus merely compensate for the iodine-induced suppression of endogenous thyroid activity and keep the indices of thyroid function at a stable level.

In any event, the thyroid glands of the thyrotoxic subjects were much less susceptible to suppression by exogenous thyroid hormone than were those of the goitrous or nongoitrous euthyroid subjects. Differentiation by this test has proven to be helpful in our clinic and is easily performed on an outpatient basis. Although in the results reported the 24-hour period was used for radioiodine accumulation, other time intervals, such as four or six hours, or the use of the "accumulation gradient," should be just as satisfactory (2).

TECHNIQUE OF THE THYROID SUPPRESSION TEST

It is recommended that the test be performed by first determining the radioiodine uptake without treatment. Then a dose of 180 mg. of desiccated thyroid is given daily for from one to two weeks and the uptake re-determined, correcting for residual thyroidal radioactivity. If the uptake is suppressed below 20 per cent, it indicates that thyroid function is normal. If it is not suppressed below 20 per cent, a further course of 540 mg. of thyroid is given for another one to two weeks, and the uptake again determined. Suppression below 20 per cent at this level is strongly suggestive of a euthyroid state, whereas the opposite result is strongly suggestive of thyrotoxicosis. Since the great majority of euthyroid patients will show suppression of uptake below 20 per cent during administration of 180 mg. of thyroid daily for one week, in only a few patients will it be necessary to proceed with the larger dosage.

SUMMARY

The differentiation of thyrotoxic and euthyroid patients by the use of the suppressive effect of exogenous thyroid hormone on thyroidal radioiodine metabolism is described.

This test is most useful in patients who have either a thyroidal radioiodine uptake or clinical picture which is equivocal. Almost without exception, goitrous and nongoitrous euthyroid patients showed a suppression of the 24-hour thyroidal radioiodine accumulation below 20 per cent following the administration of 540 mg. of desiccated thyroid daily for one or two weeks; in fact, the uptakes of most of these patients were suppressed below 20 per cent by only 180 mg. daily. In none of the thyrotoxic patients was suppression below 20 per cent induced by a dosage of 540 mg. daily and in only 1 was such suppression induced by 720 mg. daily.

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APPENDIX—REPRESENTATIVE CASE HISTORIES

Thyrotoxic patients

I.S. was a 35-year-old colored woman with shortness of breath, palpitation, swelling of the feet and some precordial pain for three months. She had had hyperphagia with a concomitant weight loss of 9 to 10 pounds, slight tremor of the hands, enlargement of the thyroid gland and amenorrhea for the preceding four months. Her pulse was 120, blood pressure 160/76, and weight 112 pounds. The skin was warm and moist. No eye signs of thyroid disease could be detected. The thyroid gland was diffusely enlarged, slightly more on the right side. There was a fine tremor of the tongue and of the fingers. The heart was slightly enlarged with a very forceful thrust. The serum cholesterol level was 115 mg. per 100 ml. The initial thyroidal radioiodine uptake was 73 per cent. The patient was given 180 mg. of thyroid daily for two weeks and then 360, 540 and 720 mg. per day for one week each. There was no appreciable change in her radioiodine uptake and at the end of the final week of medication with 720 mg. of thyroid per day, uptake was 81.6 per cent. There was no change in pulse, symptoms, or blood pressure during this treatment. It was believed the patient had a diffuse goiter with hyperthyroidism. She had a satisfactory remission following a course of propylthiouracil over a 12-month period.

V.W. was a 57-year-old colored woman, with congestive heart failure for at least six months and an adenomatous goiter with substernal extension. She had had decreased heat tolerance, a 25-pound weight loss, palpitation, increased sweating and polyphagia for the previous eighteen months. Her pulse was 125, blood pressure 140/90, and weight 110 pounds. The thyroid gland was irregularly enlarged to about three times normal size, with some extension below the clavicles. Several nodules could be detected in the substance of the gland. The eyes were protruding, and there was some lid lag as well as difficulty with convergence. Initial radioiodine uptake was 66 per cent. She was given increasing doses of thyroid at weekly intervals, up to 720 mg. per day. At the end of that time the uptake was 49 per cent. The patient had a subtotal thyroidectomy and eight months later had no further difficulty with congestive failure, palpitation or increased sweating. Her weight had increased 20 pounds.

M.Q. was a 46-year-old colored woman, with a one-year history of heat intolerance, nervousness, thyroid enlargement and cardiac decompensation. Her pulse was 140, blood pressure 152/70, and weight 120 pounds. The thyroid gland was diffusely enlarged to about twice normal size, with a marked bruit over both lobes; and there was moderate exophthalmos, with lid lag. A marked tremor was present. The heart was enlarged and showed a very forceful apex impulse. The initial thyroidal radioiodine uptake was 100 per cent. The patient was treated with increasing doses of thyroid daily up to 720 mg. per day, at the end of which time the uptake was 78 per cent. She was then treated with

a therapeutic dose of radioactive iodine and by the end of six months had a complete remission.

A.R. was a 46-year-old white man, who had had a thyroidectomy for toxic goiter six years previously, following a one-year history of increasing nervousness, insomnia, tremor, weakness and weight loss. He had felt well until nine months before admission, when weight loss, weakness, increased sweating, palpitation and tremor again became marked. His pulse was 115, blood pressure 130/70, and weight 148 pounds. The skin was warm and moist, and there was mild exophthalmos with no ophthalmoplegia. A transverse cervical scar was evident, and the thyroid showed a slight, very firm enlargement which appeared more marked in the right lobe. No thrill or bruit was detectable. The heart was not enlarged but the impulse was quite forceful. There was a marked fine tremor of the hands. The initial radioiodine uptake was 98 per cent. Treatment with desiccated thyroid was instituted and increased weekly to 720 mg. daily, at the end of which time the radioiodine uptake was 88 per cent. The patient was then treated with radioactive iodine. At the end of three months myxedema had developed but it was well controlled during the subsequent eighteen months with 120 mg. of thyroid daily. It was felt that the patient had recurrent hyperthyroidism following a subtotal thyroidectomy, with an adequate remission subsequent to radioactive iodine therapy.

Euthyroid patients

H.B. was a 47-year-old obese colored woman, with moderate angina pectoris and intermittent claudication of three years' duration. The left lobe of the thyroid gland was known to have been enlarged to about twice normal size for at least two months. There had been no recent weight loss, hyperphagia, increased sweating, or palpitation. Her weight was 195 pounds, pulse 84, and blood pressure 140/90. The left lobe of the thyroid gland was diffusely enlarged to about twice normal size but there was no thrill or bruit. Thyroidal radioiodine uptake was 48 per cent. The patient was given 180 mg. of thyroid a day for one week. Her radioiodine uptake at the end of that time was nil. Medication with thyroid was not continued. The patient was last seen one year later and there had been no essential change in her condition or appearance.

B.W. was a 25-year-old white woman, who had been found to have a small goiter six months previously. She was otherwise without complaints. Her weight was 124 pounds, pulse 72, and blood pressure 118/70. The thyroid gland was diffusely enlarged to about twice normal size. There was no thrill or bruit. The results of physical examination were otherwise not remarkable. Thyroidal radioiodine uptake was 36 per cent. Following the administration of 180 mg. of desiccated thyroid for one week, the radioiodine uptake had dropped to 3 per cent. Treatment with thyroid was not continued. The patient was last seen seven months later, at which time she was still without complaints and the goiter was unchanged in size.

R.E. was a 38-year-old colored man who had been known to have a goiter for at least fifteen years. It had not been enlarging prior to admission, and he had no complaints other than occasional fatigue and insomnia for the previous three years. His weight was 172, pulse 82, and blood pressure 144/86. The thyroid gland was enlarged to about twice normal size, and was firm, and slightly irregular in outline. The findings on physical examination were otherwise not remarkable. Thyroidal radioiodine uptake was 40 per cent. Following the ingestion of 180 mg. of desiccated thyroid daily for one week, the uptake had fallen to 8 per cent. Treatment with 360 mg. daily for another week resulted in further suppression of the uptake to 5 per cent. Treatment with 180 mg. of thyroid was then continued for eight months, at the end of which time the thyroid had regressed until it was barely palpable.

R.S. was a 42-year-old colored woman who had been troubled by obesity for approximately twenty years. A small goiter had been found two weeks previously. Her weight was 254 pounds, pulse 82, and blood pressure 184/108. She was grossly obese and had a very small diffuse goiter without thrill or bruit. There were no eye signs of thyrotoxicosis. The skin was warm and dry, and there was no tremor. The heart sounds could not be heard and the cardiac impulse was barely palpable. Thyroidal radioiodine uptake was 38 per cent. Following ingestion of 180 mg. of thyroid daily for one week, it had fallen to 12 per cent. The patient was given 540 mg. of thyroid for another week, at which time the uptake was 8 per cent. Treatment with thyroid was then discontinued and the patient was last seen one year later. There had been no change in her physical appearance or symptoms.

Patients in whom the diagnosis was facilitated by the thyroid suppression test

E.H. was a 36-year-old, colored woman with complaints of dull ache in the lower substernal and lumbar region, headache, palpitation, profuse perspiration, weakness, easy fatigability, exertional shortness of breath, paroxysmal nocturnal dyspnea, occasional swelling of the ankles, nervousness and irritability for the previous two years. Her pulse was 108, blood pressure 200/120, and weight 142 pounds. There was a slight nontender enlargement of the isthmus of the thyroid gland, and a fine tremor of the fingers. The heart beat was forceful and there was 2+ pitting edema of the ankles. The initial thyroidal radioiodine uptake was 46.8 per cent. The patient was given 180 mg. of thyroid for one week, following which the radioiodine uptake had dropped to 10.7 per cent. She was then given 360 mg. for another week and the uptake dropped further to 6.8 per cent. There was no change in vital signs or symptoms during therapy with thyroid. The patient was given a trial of propylthiouracil, 100 mg. every eight hours for seven weeks. No change was induced in any of her symptoms or physical signs at the end of this period. It was concluded that the patient had hypertensive heart disease and a small goiter, but was euthyroid.

L.A. was a 36-year-old colored woman who had had a nodular goiter for at least eight months. She complained of nervousness and some heat intolerance. Her pulse was 82, blood pressure 140/80, and weight 136 pounds. The skin was cool, and there was a slight coarse tremor of the hands. The thyroid gland was about three times normal size and rubbery, with eight to ten easily palpable nodules in the substance of the gland. The initial thyroidal radioiodine uptake was 75 per cent. The patient was given 180 mg. of thyroid a day for one week, following which the radioiodine uptake was 12.2 per cent. She was then given 360 mg. a day for another week, at which time the uptake was 8.4 per cent. She was then continued on 240 mg. of thyroid daily for two months, at the end of which time the goiter had completely disappeared. There had been no change in her signs or symptoms during therapy. It was concluded that the patient had a hyperplastic nontoxic nodular goiter, which underwent complete remission during administration of desiccated thyroid. Thyroid therapy was then stopped for three months, following which the goiter reappeared and enlarged to approximately its former size. Reinstitution of therapy with thyroid again caused the goiter to disappear completely.

L.M. was a 28-year-old white woman who had had known thyroid enlargement for eight years. For the two or three years prior to admission she had felt weak and tired and had experienced some cold intolerance. Her pulse was 82, blood pressure 130/76, and weight 140. Her heart was not enlarged and the impulse was of normal intensity. The thyroid gland was diffusely enlarged to about twice normal size, but there were no eye signs or tremor. The initial thyroidal radioiodine uptake was 60 per cent. The patient was given 180 mg. of thyroid for one week, at the end of which time her uptake was 5.1

per cent. Treatment with 180 mg. of thyroid daily was continued for three months, at the end of which time the goiter had almost completely regressed in size. It was believed that the patient had a nontoxic diffuse thyroid enlargement.

E.R. was a 39-year-old white woman with a history of nervousness, decreased cold tolerance, poor appetite, a 10-pound weight loss, constipation and general lethargy for nine months. Her pulse was 90, blood pressure 110/70, and weight 142. The skin was cool and moist. There was a very slight tremor of the hands. The thyroid gland was diffusely enlarged to about twice normal size, but there was no thrill or bruit, and no eye signs. The heart was not enlarged but the impulse was forceful. The initial radioiodine uptake was 52 per cent. The patient was treated with 180 mg. of thyroid daily for one week, and then with 540 mg. daily for two weeks, at the end of which time her uptake was 60 per cent. Treatment with propylthiouracil was then instituted and at the end of five months the patient had had a good remission of all her symptoms and had gained 12 pounds in weight. It was felt that the patient had diffuse goiter with hyperthyroidism.

W.J. was a 30-year-old colored man who had been blind since the age of 11, following injury to his eyes. He had complained of being nervous for the previous four months. He attributed this in part to the fact that his wife had become aware of his marital infidelity and that he had spent two months in jail for petty larceny. His appetite had decreased somewhat during this time and there had been a weight loss of about 5 pounds. He complained of occasional palpitation when he became excited, and occasional tremor. The thyroid gland had been noted to be enlarged for the previous three weeks. His weight was 187 pounds, pulse 90, and blood pressure 128/85. There was intense corneal scarring on both eyes but no eye signs of Graves' disease. The thyroid gland was diffusely enlarged to about two or three times normal size, more on the left; there was no thrill or bruit. The heart was of normal size and the beat was not forceful. There was a very slight tremor of the extended hands. The skin was cool and dry. The thyroidal radioiodine uptake was 56 per cent. The patient was given 180 mg. of thyroid daily for one week, at the end of which time the radioiodine uptake was again determined and found to be 5 per cent. The patient was treated with thyroid for a period of three months, at the end of which time the goiter had decreased to approximately one quarter of its original size. The nervousness and palpitation improved greatly during the period of treatment with thyroid, although the patient still had palpitation occasionally when he became excited or upset. He was last seen nine months after the first visit, having discontinued treatment with thyroid six months previously. The thyroid gland was still about one quarter its initial size and his symptoms and physical appearance had not changed appreciably since the last visit. It was felt the patient had a nontoxic diffuse goiter.

OF BOILING OIL AND BARBERS' CHAIRS*

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SHORTLY before his death, Sir Isaac Newton said, "I do not know what I may appear to this world, but to myself I seem to have been only like a boy playing on the seashore and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me."

Goiter has been reported as existing since the beginning of the human race. It was first recorded in the East Indies two thousand years before Christ. It was not until 939 A.D., however, that the first attempt to cure goiter by surgery was made and recorded.

Hippocrates is known to have considered goiter as a deformity of the body and in his Lib. de Glandulis he stated that, "Most diseases of the glands are not primary within themselves and when the glands of the neck become diseased of themselves, they become tubercular and produce struma and the body is attainted with fever. If it be the pituitous, and much in quantity and the fluxion is slow, then they become inflamed, and the inflammation with stasis of the humor exists generating the worst form of struma." In his Lib. de Affectionibus he said, "Fevers and strumae, lumps, bile, and carbuncles arise from the pituitous humor and to whomso-ever is of the bilious nature I give this treatment. He who is bilious is purged of bile, if he be pituitous he is purged of his mucus, and if he be atrabilious, of his black bile, if hydropic of his water."

Aristotle gave a very accurate description of the structures of the neck but did not make mention of any which, even later, were thought to be the thyroid gland.

Celsus was the first among the pre-Christian authors to attempt to make distinction between the various forms of tumors of the neck. He did not present a clear classification but did try to distinguish struma from other tumors such as cysts, lipomata and bronchocele. He described struma as a tumor "under the skin between the skin and the larynx which is

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fleshy only, or may contain a sort of honeylike substance, sometimes even containing small bones and hairs fixed together." For the cure of these tumors he recommended that "a straight incision be made in the midline of the neck and the fluid be removed," if the tumor contained fluid. If it were of the fleshy type it was to be "pulled out of the wound with the hand and the wound then treated with liniments."

Vitruvius a famous architect who practiced during the reign of Emperor Augustus apparently was familiar with goiter as an entity. During a discourse on the subject of "aqueducts and potable waters" he noted that some of these waters contained nitre which, because of its purgative qualities, diminished the size of strumae or goiters in the people who drank of it. "Praesituam vero facultatum nitritis in purgationibus ut strunarum quoque inflationes comminuent."

Galen (128–201) in his extensive writings mentioned various tumors of the neck and in Book IV, (Cap. 6.) De Locis Affectis, he described in considerable detail the recurrent laryngeal nerve, presented various theories as to its function, warned against cutting it, and spoke of large tumors of the neck which pressed upon the windpipe and caused aphonia, but apparently did not recognize these as being tumors of the thyroid gland.

Paulus Aeginitae, Lib. VI, Cap. XXXV, described a tumor in the neck which was probably goiter, as follows: "Struma which the Greeks called Choeras, is a hardened gland growing principally in the neck or others in the groin. The name in Greek refers to hogs since they are prolific and bear many offspring (pigs) or since they have glandulous necks." The treatment as suggested by him was as follows: "Also the bigger strumae being lifted out with hooks and suspended, the membranes everywhere surrounding them are to be separated and the tumor removed. With the utmost care we should see to it that neither the arteries which are called the carotids nor the recurrent nerves are injured. And if some vessel interferes with the work it is to be bound about by a cord, or cut through the middle unless it be too large. Now when we have reached the narrow base of the struma, the one to the right is to be first cut off, and then with the index finger deep down in the wound we are to try to find out if there are other strumae close by, which in the same manner may be turned out. But if we believe that there is any great vessel or even many, deep down in the struma, we are not to cut it away from its base, but it is to be bound about with a cord and at a point above any danger excise it freely and then with medicines applied on linen the cure is to be attempted. If it be cut off we must draw the edges together so that they are everywhere in contact and if there be no superfluity of tissues, fasten them together with pins. But if there be too much flap after the removal of the struma we bring it together in the shape of a myrtle leaf and sew it with sutures and inject healing or stimu-

lating medicines." This procedure, which was described in the 7th century, certainly seemed to be that of thyroidectomy.

Mundinus (1260–1325) was one of the most prominent anatomists of the mediaeval period. He described the recurrent nerves ("the nervi reversivi") as follows: "and these then are called the nerves of the voice or reversive nerves, since indeed they are the principle things in the origin of the voice." Haley Abbis in his Liber Totius defined their purpose, described their arrangement as recurrent, and said "they are the origin of great motion and hence strong and thick, since they must be strong and hard for the harder the nerve the greater force it exercises. These nerves begin in the soft tissues of the brain, and the longer they are the harder they become, so they first pass to the heart and then loop back of the glottis, growing harder as they grow longer. And further the nerve must be looped to the heart and back again, because the voice springs both from the heart and the brain."

Bartholin (1616–1680) in his Anatomy (1670, Tabula II, page 347) gave a very detailed but very inaccurate illustration of his conception of the thyroid gland. Ver Heyen (1648–1710) pictured the gland with its apices pointing downward and called it the laryngeal gland.

It was Wharton (1610–1673) who first described the gland more or less correctly and who gave it its name, which came from the Greek word meaning a shield. He described it as consisting of two lobes connected by an isthmus but was unable to determine whether or not it had an excretory duct.

In 1761, Morgagni pointed out the necessity of autopsies for advancing the knowledge of the various pathologic states of the thyroid. Fichte argued that advancement in comprehending the different diseases which were caused by goiter lay within the realm of the basic sciences. Desault, Corvisart, Bichat, Dupuytren, Laennec and others in France studied the problem with this in mind and made valuable contributions concerning the function of the thyroid. Cretinism became associated with endemic goiter. Ord coined the name "myxoedema." Sir William Gull set up commissions to study this disease. Cruveilhier, in 1835, after much painstaking work and dissection, announced that the thyroid had no excretory duct. This fact was promptly verified by reports of other anatomists.

About 1788 Flajani recognized that palpitation of the heart and "exitu oculorum" had some relation to the presence of goiter. Parry, in 1815, gave a very commendable description of exophthalmic goiter. He studied and recorded 8 cases in detail. In 1835, Robert James Graves of Dublin, who is the patron saint of this organization, was the first to correlate properly the symptoms of exophthalmos, rapid heart, loss of weight, tremor of the hands and nervousness, to a tumor of the thyroid.

In 1849, the chemist Chatin investigated the iodine content of air, water and soil and related these observations to the development of goiter. As a result of his studies, in 1855–1870, a law was passed in France making it compulsory to add iodine to the food and water. However, little interest was aroused within the medical profession until Graves and Basedow, as previously mentioned, described the pathology of the various types of disease within the thyroid gland, and clearly defined and differentiated exophthalmic goiter from myxedema.

In spite of these important discoveries, which began in 1700, the treatment of goiter was still unsatisfactory. Operation was performed as a last resort, and then only to prevent suffocation from pressure of the tumor upon the trachea. The nonsurgical attempts to cure the disease were many and varied. Some were disastrous. All were unsuccessful. Pliny in his Natural History mentioned 69 various remedies that had been proposed for the cure of struma. These ranged from honey to the distillate of snakes; from feces of different animals and reptiles to the brine and shells found in the ocean and on the beach. The fat of the goat and the oil of the toad were boiled and, after placing the patient in a barber's chair with the neck extended, were injected directly into the thyroid gland. The root of oxyalys hung around the goitrous neck was occasionally reported to have effected a "cure." Cardanus (1501–1576) recommended "the drinking of a distillate of human feces" for its cure.

Jean Baptiste Verduc in his book on surgical pathology published in 1720 reported the case of a peasant in Switzerland who had a goiter so large that it hung down over his chest and produced severe pressure symptoms. He went to a blacksmith to have his horse shod. The blacksmith heated an iron poker redhot. He turned quickly away from the forge, lost his balance, and accidently thrust the hot poker into the neck of the peasant. The contents of the goiter were promptly evacuated. Suppuration followed and the goiter disappeared. All sorts of foreign bodies, such as wicks, setons and hair-setons were placed within the goiter. Strings and even pliable vines were used to wind around the goitrous tumor, with the hope of strangulating it and reducing its size. Following these procedures strong caustics were introduced into the gland itself.

During the 18th century, continued but unsuccessful attempts to remove goiters were being made. The immediate mortality was usually due to hemorrhage, and most of those who did survive the operation died of sepsis. However in 1791 Desault reported a successful total extirpation of the thyroid gland. J. A. Hedenus of Dresden, in 1821, recorded 6 cases operated upon without a death.

Victor v. Bruns, 1841–1864, reported 6 deaths in a series of 28 goiters removed. Billroth of Zurich, in 1867, had such a forbidding mortality

and became so discouraged with his results that he advised that no more goiters be operated upon.

However, in spite of this admonition, it was evident that surgery was the treatment of choice, if hemorrhage and infection could be controlled. It only remained for someone to master the technic which would prevent these complications.

In 1866, Paul Shick reported the survival of a 10-year-old boy after the removal of a large goiter. However, several months afterwards the boy lost his normal mentality and became a typical cretin. The transformation was explained on the theory that the blood supply to the brain had been cut off. Many other similarly distressing results were reported by various surgeons. It is no wonder, then, that the injection of boiling oil and caustics again came into common use.

During this era of surgical frustration, uncertainty and failure there came Theodor Kocher. The solution of these perplexing problems required someone "with his nobility of character, his artistic talents, with his enormous capacity for work, his passion for the truth of things, with his wonderful judgment, evergrowing and selfcontrolled by constant sustained study and restudy of patients and results. He slowly and solidly grew to be the colossal figure to be held by his pupils and followers in the wide-world with overpowering admiration."

The story of Kocher is well known to all of us. He accepted the solution of the goiter problem as a challenge, and attacked the problem basically. He visited famous clinics abroad and realized that hemorrhage was still the greatest immediate hazard. He observed the master surgeons at work and readily detected their shortcomings. After returning home he spent several years in his laboratory, and then, between 1872–1874, he operated upon 13 patients. Six operations were performed for dyspnea, 5 for rapid growth of the tumor and 2 for "inflammation" which developed within the thyroid gland. The incision used was one in the midline of the neck. The technic consisted in slowly developing flaps, dissecting out the gland and tying off each vessel as it presented. At the end of the operation, the fascial layers at the bottom of the cavity were sutured to the skin edge. The wounds were left widely open. In spite of this procedure, 2 patients died of infection.

Case No. 9 in Kocher's series was Marie Birchsel, 11 years old, who had a large goiter and was operated upon August 1, 1874. The gland was totally excised. The child was well for several weeks and then became dull, lazy and unintelligent. Kocher was so discouraged with this result that between March 3, 1874 and July 21, 1877, he operated upon only 5 other cases.

He undertook an occasional case, however, and on March 25, 1881 he operated upon his forty-fourth patient, performing a total extirpation of

the thyroid. A letter from the patient's physician said, "Your operation was a success; the evil of the neck is gone. However, she has not had a good hour since. She complains, constantly, of freezing and her limbs have no feeling and her abdomen is swollen."

Kocher was not satisfied with the surgical approach which was being used and after operating on 59 cases with the median incision he developed the collar type or so-called "Kocher incision."

Beginning with the fifty-ninth case and including the one hundred and second case, he lost 5 patients. It was now evident that the thyroid could be removed with a reasonable degree of safety and with a relatively low mortality. However, he was still disturbed and discouraged by the reports which he received concerning the symptoms of cretinism, which often developed several years following surgery. He, therefore, called back for a follow-up study all of the patients operated upon for goiter, with whom he could get in contact. Eighteen of them returned. He noticed that 2 of these 18 had persistent or recurrent nodules in the gland, but they seemed to be in a state of good health. No residual thyroid gland could be found in the remaining 16, but each of these presented symptoms which were far from satisfactory. Many were worse than before the goiter had been removed. The younger patients had retardation of their physical and mental development. The older patients, although the physical development was unimpaired, complained of drawing, aching pains in the arms and legs. This was followed by extreme weakness and fatigue. Later they became sensitive to cold. The legs and arms became blue, swollen and easily frostbitten during the winter.

The mortality following subtotal thyroidectomy for endemic goiter in the hands of a few accomplished surgeons was, at this time, not prohibitive. However, the death rate following surgery which was beginning to be undertaken for toxic diffuse goiter was so appalling and the results so disastrous that it caused the operation to be shunned by both patient and physician.

Although the value of iodine as a prophylactic measure against endemic goiter had been well established for a great many years, it was not until 1922 that Henry Plummer of our own organization introduced iodine as a means of preparing patients with toxic diffuse goiter for operation. The results of his discovery and the reduced mortality rates following its use were so dramatic that the surgical treatment of goiter was completely revolutionized, so much so that this has properly been called, the "Iodine Era." During this period many of the founders of this organization became pioneers in the surgical treatment of goiter and obtained not only a national but an international fame for their accomplishments in this field.

In 1909 Kocher received the Nobel Prize for the discovery and descrip-

tion of the function of the thyroid gland. Halsted, in our country, was one of the first to describe the histopathology of toxic diffuse goiter and to call attention to the fact that it required several weeks for the full effects of iodine to manifest itself within the toxic gland. Kocher reported a mortality of 8 per cent in 24 cases of exophthalmic goiter and C. H. Mayo reported a mortality of 6 per cent in 234 cases of exophthalmic goiter. The mortality rate remained at these high levels for only a very brief time, however. In 1910 Kocher reported 4,629 thyroidectomies with an over-all mortality of 3.2 per cent. In 1914 C. H. Mayo reported 6,960 operations on the thyroid, of which 3,327 were for toxic goiter; the mortality rate was between 1 and 3 per cent.

In 1922 Crile reported on his method of "stealing" goiters. He performed 1,783 such thyroidectomies, of which 1,022 were for exophthalmic goiter, with a mortality rate of 1.4 per cent. In the same year Pemberton reported for the Mayo Clinic 1,954 cases of all types of goiter with an over-all mortality of 1.8 per cent. In 1935, thirteen years after the introduction of the preoperative use of iodine, C. H. Mayo and Pemberton reported the mortality rate for all goiters operated upon from 1923 to 1934 to be 0.88 per cent.

Halsted, before giving up his work, said "There are operations today more delicate, and perhaps more difficult, but they have followed naturally and easily in paths made clear for them. But is there any operative problem propounded so long ago, and attacked by so many, which has cost so much thought and endeavor and so many lives before its ultimate solution was achieved, and further, is there any problem in surgery having required for its solution such intrepid throbbing and prolonged striving of the world's greatest surgeons which has yielded results so bountiful and so adequate?"

For thousands of years attempts to cure goiter by surgery were fraught with such disastrous results that it was, at various times, almost given up. At present, even though surgery has reached the acme of perfection in dealing successfully with the resting-place of the disease, namely, the thyroid gland, little is known of the actual cause of goiter.

The surgical treatment of goiter is not to be discarded. The technic of thyroidectomy has been perfected, the mortality is almost negligible, and the morbidity is minimal. Little, if any, more can be accomplished, so far as the cure of goiter is concerned, from this standpoint. Still, like the boy on the beach gathering pebbles—the vast ocean of mystery, knowledge and truth has, as yet, not been conquered. The conquest of this lies not within the realm of surgery but within the realm of research and investigation; within the realm of the laboratory; within the realm of those unheralded men who may perhaps not even come in contact with the victims of the disease but who are, nevertheless, dedicating their lives to the solution of

this problem. It is to this group that we must look for the answer to the cause, and thence to the ultimate cure of goiter. Perhaps it will not be surgery. We, the members of this Association will be the first to acclaim and welcome the discovery, be what it may.

Were this not true the very existence of the American Goiter Association would not be justified. Meantime, the clinician and the research worker will advance hand-in-hand. Each will always do that which is in the best interests of the patient.

We pass quite naturally then into the present era in the study of goiter—the era of biological chemistry and its allied sciences, as they relate to the etiology of the disease.

Is it not, therefore, in keeping with this era that the membership of this organization is gradually adding more and more investigators to its ranks? Well do we realize that there are nonsurgical treatments which are beginning to play a part in the cure of toxic diffuse goiter. Thus far, however, nothing has been presented that will take the place of surgery in the treatment of nodular goiter.

The days of boiling oil and barbers' chairs have given way to the aseptic scalpel and the modern operating room. We, the surgeons of today, have mastered the technic by knowledge well learned. Our colleagues, the investigators, will some day discover the cause, by wisdom well applied. Knowledge is proud that he knows so much. Wisdom is humble that he knows no more.

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AN EXOPHTHALMOS-PRODUCING SUBSTANCE IN THE SERUM OF PATIENTS SUFFERING FROM PROGRESSIVE EXOPHTHALMOS*

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IN A recent publication from this laboratory (1) the separation of the exophthalmos-producing substance (EPS) and the thyroid-stimulating hormone (TSH) of the anterior pituitary was described. In this previous investigation a crude quantitative assay for EPS was made, using the common Atlantic "minnow," *Fundulus heteroclitus, Linn.* (2), as the test object. It has been observed that these fish under proper conditions will respond with measurable exophthalmos when a dose as small as 15 micrograms of a dry EPS preparation is given.

During the past several years, while the foregoing studies were in progress, efforts were simultaneously made to demonstrate an exophthalmos-producing substance in the serum of patients suffering from the severe or progressive exophthalmos sometimes associated with Graves' disease. Recent success in demonstrating EPS in human serum has prompted this preliminary report.

METHODS

Funduli in groups of 8 to 12 were placed in stainless-steel tanks containing fresh water at a temperature of 65° to 70° F. Colored thread was placed through, and tied in the lower lip of each fish so that individual identification was possible. The intercorneal distance on each fish was measured to 0.1 mm. by means of an improved caliper method modified after that described by Dobyns (3). Such measurements were made on each fish before, and at intervals of six to twenty-four hours following the administration of the material to be tested. The degree of exophthalmos was calculated as the percentage increase in the intercorneal distance in each fish. Each series of measurements was made by the same observer. In some instances a second series of measurements was made on the same fish by a different observer. A comparison of two sets of measurements on the same fish revealed that variations of more than 0.3 mm. between the two observers were

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very rare. Since, in the fish used, the initial intercorneal distance was about 11 mm., the accuracy of measurements of the change in intercorneal distance was usually within 3 per cent between two readings. In plotting a complete series of measurements on a single fish during the development of exophthalmos, any error of more than 3 per cent was usually recognizable.

The material to be tested was injected into the coelomic cavity of the fish by introducing a #26 needle through the vent and the wall of the bowel. Since these fish are relatively small, the volume of fluid that could be injected was limited to 0.25 ml. in a single injection. Because of this limitation, the material to be assayed (whole human serum) was given in three injections at intervals of eight to sixteen hours. This volume rarely altered the behavior or caused the death of the fish.

Several control observations were made. Some groups of fish were injected with amounts of pooled normal human serum equal to that of the serum being tested. There were 24 fish in which three different pools of serum were used. Other groups of fish were injected with a known amount of a standard pituitary extract (dissolved in 0.25 ml. of physiologic sodium chloride) known to be rich in the exophthalmos-producing substance. This was to test the degree of responsiveness of the fish. Final groups were injected with 0.25 ml. of physiologic sodium chloride, which was the vehicle for the EPS standard.

A brief résumé of the clinical features of each of the 6 patients whose serum was tested and found to contain an exophthalmos-producing substance is given with the legends for Figures 2 through 7. For clinical reasons, the importance of assessing the status of severe exophthalmos has been emphasized (4), *i.e.*, whether progressing actively (and at what

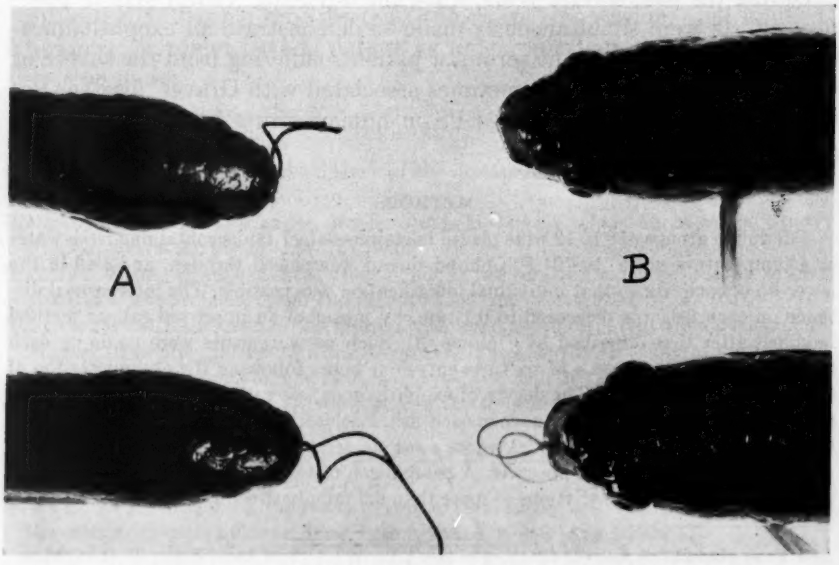

FIG. 1. Exophthalmos produced in Funduli by the administration of 0.75 ml. of serum from a patient with severe progressive exophthalmos.

A. Normal Funduli

B. Funduli after receiving serum from Patient 3 (see Fig. 4).

rate), stationary or regressing. Similarly it has seemed important to make such an assessment of the disease in the patients studied, because one might expect to demonstrate a causative factor more readily in a patient with mild but active disease than in a patient with long-standing, stationary, severe exophthalmos.

RESULTS

The serum from most of the patients produced gross exophthalmos that was clearly evident without the use of a measuring device, as shown in Figure 1. In other instances the exophthalmos, though less obvious, could be demonstrated by measurements (Figs. 2–7).

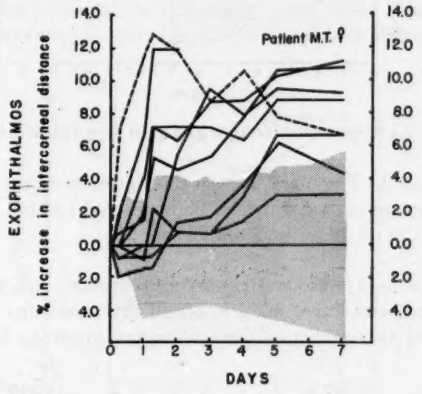

FIG. 2. The individual responses among a group of Funduli which had received serum from Patient 1.

In this and all subsequent figures the broken line on the graph represents the mean increase in intercorneal distance of 8 or more fish which had received a single injection of 0.25 mg. of a standard pituitary extract known to be rich in EPS. The shaded area represents the maximal change from the initial reading of all 24 control fish which had received pooled normal human serum in the several experiments described. The solid black lines in this figure represent the percentile change in intercorneal distance of each fish which had received (within the first twenty-four hours) three doses of 0.25 ml. of serum from Patient 1.

Patient 1. M.T., female 32. This patient had noticed prominence and irritation of the eyes for six months and very mild symptoms of thyrotoxicosis for four months before the serum was obtained for study. This history indicated that propylthiouracil administered during a 3-month period had caused the basal metabolic rate of +20 to fall to −20 per cent. At the time the serum was obtained for the test, Lugol's solution was the only medication being given. Although both eyes were moderately prominent, it was reported that no significant measurable increase had occurred in the preceding three months. There was injection of the conjunctival veins, irritative discomfort about the eyes, and incomplete approximation of the lids of one eye on gentle closure. There was no extraocular muscle weakness. Although the eye problem might be considered as being stationary, the disease should be regarded as being in the early phase.

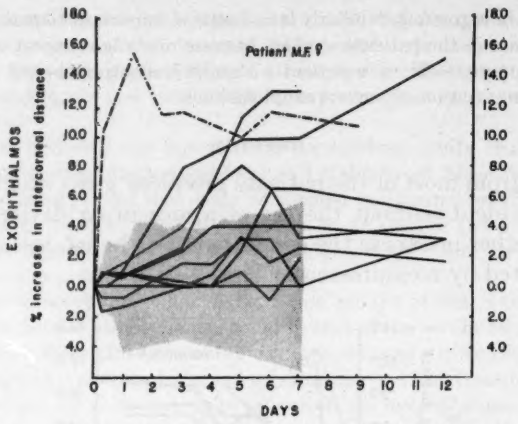

FIG. 3. The individual responses among a group of Funduli which had received serum from Patient 2.

(See legend to Figure 2.) The black lines in this figure represent the percentile change in intercorneal distance of each fish which had received (within the first twenty-four hours) three doses of 0.25 ml. of serum from Patient 2.

Patient 2. M.F., female, 41. Moderately severe thyrotoxicosis, without symptoms referable to the eyes, had been corrected by subtotal thyroidectomy two years previously. Diplopia, accompanied by swelling of the eyelids and proptosis began in the right eye

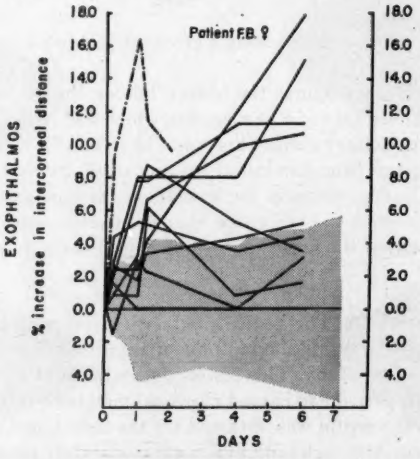

FIG. 4. The individual responses among a group of Funduli which had received serum from Patient 3.

(See legend to Figure 2.) The black lines in this figure represent the percentile change in intercorneal distance of each fish which had received (within the first twenty-four hours) three doses of 0.25 ml. of serum from Patient 3.

ten months after the operation. This was followed by similar symptoms in the left eye five months later. At the time serum was obtained for this study there was marked prominence of both eyes, with swelling and tenderness of the periorbital tissue and a scratchy sensation in both eyes. There was some extraocular muscle paresis bilaterally. Significant laboratory tests were reported as follows: BMR +25 per cent; I^{131} uptake by the thyroid, 16 per cent in twenty-four hours. The exophthalmos in this patient was regarded as being in the active phase, having been progressive over a 14-month period.

Patient 3. F.B., female, 65. A thyroidectomy had corrected symptoms of thyrotoxicosis at the age of 45. Progressive exophthalmos began many years after the operation and progressed rapidly, so that an orbital decompression had been required to save the eyes. After very slight temporary improvement, progression of the exophthalmos began again and, shortly after this test was made, further surgical decompression was required. At the time serum was obtained for this study, great blebs of edematous bulbar conjunctiva hung from between the lids of both eyes and loss of vision was imminent.

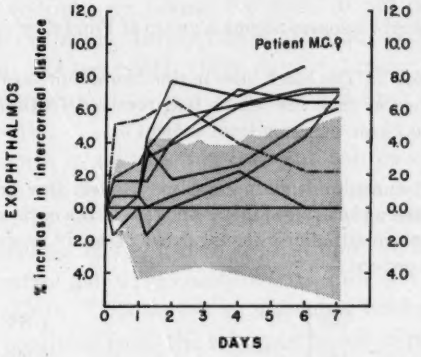

FIG. 5. The individual responses among a group of Funduli which had received serum from Patient 4.

(See legend to Figure 2.) The black lines in this figure represent the percentile change in intercorneal distance of each fish which had received (within the first twenty-four hours) three doses of 0.25 ml. of serum from Patient 4. It should be noted that in this experiment the response of the fish to the standard pituitary preparation was rather poor, whereas the response in several of the experimental fish exceeded the standard.

Patient 4. M.C., female, 24. One year before serum was obtained for this study, exophthalmos began to develop. A thyroidectomy four months thereafter resulted in some improvement in the eye problem. Progression of the exophthalmos had recurred to the extent that an orbital decompression was required at the time this test was made. The patient was in a euthyroid state and the BMR was reported to be −4 per cent. The disease in this patient was classified as active and severe.

Patient 5. F.S., female, 61. Lacrimation, a sense of irritation and venous congestion of both eyes accompanied by rather mild symptoms of thyrotoxicosis began one and a half years before serum was obtained for this study. After these symptoms had been present for six months, the hyperthyroidism was corrected by radioiodine therapy. During the preceding year there had been an increase of 3½ mm. in the prominence of both eyes. A sense of resistance to backward displacement of the eyes had become apparent to the

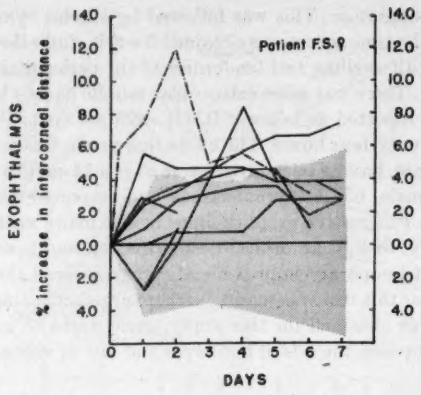

FIG. 6. The individual responses among a group of Funduli which had received serum from Patient 5.

(See legend to Figure 2.) The black lines in this figure represent the percentile change in intercorneal distance of each fish which had received (within the first twenty-four hours) three doses of 0.25 ml. of serum from Patient 5.

examiner and mild chemosis and photophobia developed. One grain of desiccated thyroid per day had maintained the basal metabolic rate in the euthyroid range. At the time this test was made the exophthalmos was regarded as slowly progressive. No extraocular muscle weakness was present.

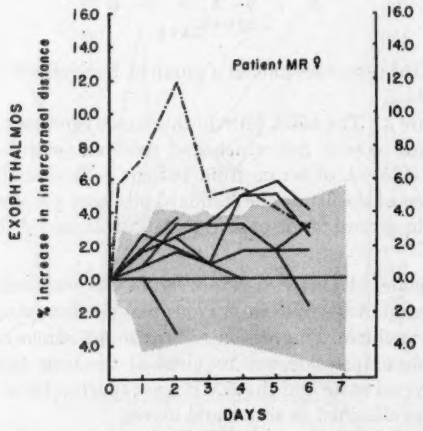

FIG. 7. The individual responses among a group of Funduli which had received serum from Patient 6.

(See legend to Figure 2.) The black lines in this figure represent the percentile change in intercorneal distance of each fish which had received (within the first twenty-four hours) three doses of 0.25 ml. of serum from Patient 6.

Patient 6. M.R., female, 40. Beginning several months following subtotal thyroidectomy, prominence of the eyes, puffiness of the lids and lacrimation progressed slowly for two years. Symptoms had then become stationary or perhaps regressed slightly during the six months immediately preceding the procurement of serum for this study. Venous congestion of the bulbar conjunctiva was present and the bulging of the lids was conspicuous. There was a possibility that thyrotoxicosis was returning. From the clinical history alone it was assumed that the exophthalmos, though still troublesome, had become stationary.

To give the reader an idea of the magnitude of the measurements encountered in these experiments, the actual changes in intercorneal distance are described for a single fish among those represented in Figure 2. The most exophthalmic fish surviving at seven days in Figure 2 had an initial intercorneal distance of 12.5 mm. Thereafter the changes in this distance in the fish were as follows: six hours, 0.0 mm. (0 per cent); twenty-four hours, 0.2 mm. (1.6 per cent); thirty hours, 0.9 mm. (7.2 per cent); forty-eight hours, 0.8 mm. (6.4 per cent); three days, 1.1 mm. (8.8 per cent); four days, 1.1 mm. (8.8 per cent); five days, 1.3 mm. (10.4 per cent); seven days, 1.4 mm. (11.2 per cent).

Pooled normal serum when injected into the fish caused an increase in intercorneal distance which was seldom greater than 4 per cent (3 fish, 4 to 5 per cent; 1 fish, 5.7 per cent). Because there was essentially no variation in the responsiveness of the fish to several pools of normal serum, the data from the 24 control fish were combined to show the limits of response caused by normal serum. This serves as a shaded background in Figures 2–7. The responses resulting from the administration of physiologic sodium chloride to 24 fish fell within the limits of the responses produced by pooled normal serum. Although the fish receiving normal pooled serum occasionally showed a decrease in intercorneal distance, most of this group tended to show a slight increase; those receiving saline varied about equally above and below the zero line on the graph.

The standard pituitary extract caused a prompt appearance of exophthalmos within a few hours, as previously described (1). Following a single injection of this material, a peak of exophthalmic response was reached in about twenty-four to forty-eight hours and thereafter tended to decline. In contrast, serum containing the exophthalmos-producing substance caused the slow development of exophthalmos over a number of days.

The stability of the EPS in serum was investigated. Serum which had been sealed in sterile ampules and allowed to remain at room temperature for more than a week, was found to produce a good exophthalmic response. Moreover, the serum may be stored at $-10°$ C. for at least six weeks and retain much of its potency.

It will be seen in the illustrations that some fish responded with striking

exophthalmos, whereas others in the same tank exhibited no measurable change which was significantly different from that produced by pooled normal serum. It should be pointed out that the best EPS preparations from the pituitary very often do not cause a striking exophthalmic response in 100 per cent of the test fish. This failure may in part be due to technical problems of injection. However, the presence of an exophthalmic response in some of the fish is clear evidence that there is an exophthalmos-producing substance in the serum tested. For this reason it is probably unwise to average the response of all fish in a group until the test is better established on a quantitative basis.

DISCUSSION

During the initial part of this investigation there was repeated failure to demonstrate an exophthalmos-producing substance in the serum of patients who clinically were comparable to those described here. There are several reasons why these early trials failed. First, some of the serums may not have contained an exophthalmos-producing substance. Second, because of repeatedly observing that the exophthalmos from pituitary extracts appears in a few hours and begins to decrease by forty-eight hours, most of the experiments with serum were terminated in forty-eight to seventy-two hours, at which time the exophthalmos resulting from serum is often just beginning. Third, a single injection of 0.25 ml. of serum was originally used, and this insufficient amount of serum caused in *many* members of a group of fish an increase in intercorneal distance comparable to the greatest response occasionally seen in controls; this supported the suspicion that EPS was probably present in small quantities. Fourth, the responsiveness of Fundulus has been found to vary throughout the year. There were times when the standard pituitary preparation caused exophthalmos amounting to 25–30 per cent increase in intercorneal distance, whereas at other times the same dosage produced only a 7–10 per cent increase. Only one, or a combination of these factors might explain a failure to demonstrate the presence of EPS in serum. The first successful demonstration during this investigation occurred when the fish were responding maximally; a serum rich in EPS was available, multiple doses of serum were being tried and observations over a period as long as a week were being explored. Once the exophthalmos was demonstrated, the factors influencing success became apparent.

The availability of a reliable quantitative test for EPS in the serum of patients might be a very valuable laboratory and clinical tool. The observations described here serve to indicate that such a substance can be demonstrated in some patients suffering from progressive exophthalmos.

On the basis of the material assembled, it appears that there may be a rough correlation between the status of the exophthalmos in the patient and the degree of response in the fish. In Table 1 an attempt has been made to illustrate this possible correlation. Although progressive exophthalmos will spontaneously stop advancing, it may not do so until irreparable damage has occurred to the eyes (4). Thus it is very difficult to predict what is in store for the patient, especially when the disease is in its early period of development. Perhaps the marked exophthalmic response in fish caused by the serum from Patient 1 may be an indication of further clinical developments, even though a measurable increase in the promi-

TABLE 1

Patient	Status of patient's exophthalmos	Response in fish
1	Early phase, stationary	++++
2	Moderately severe, progressing	+++
3	Very severe, requiring orbital decompression	++++
4	Severe, requiring orbital decompression	++++
5	Moderately severe, slowly progressive	++
6	Moderately severe, stationary or regressing	+

nence of the eyes has not been detected. Perhaps also Patient 6, who had signs and symptoms that should raise great concern, is really improving. The patient's impression that the condition of the eyes had improved is in agreement with the minimal response seen in the fish.

The question may be asked whether the EPS described here in the serum of some humans is the same as that obtained from the anterior pituitary. Before such a presumptuous conclusion can be drawn it should be pointed out that the material from the pituitary causes a response very promptly, whereas that from serum usually causes a response after several days. If the pituitary preparation is added to serum and the mixture administered to the fish, the response is rather prompt. In this laboratory a method has been devised for recovering the EPS fraction (of pituitary origin) after it has been added to serum. Although this fraction may be separated from some of the proteins of the serum, the application of the same chemical procedure so far has not served to separate the naturally occurring material from whole serum. This observation, in addition to the apparently slow absorption of the serum EPS from the coelomic cavity of the fish, suggests that there may be a difference in structure, not necessarily between the active substances but between the substances to which they may be attached.

SUMMARY

An exophthalmos-producing substance has been demonstrated in the serum of some patients suffering from severe or progressive exophthalmos. Fundulus, an Atlantic "minnow," when injected with the serum responded with a measurable increase in intercorneal distance. The data obtained suggest that there may be some correlation between the degree of response in the fish and the stage and severity of the patient's exophthalmos.

Acknowledgment

The authors wish to thank Drs. E. J. Ballintine, S. F. Haines, R. W. Schneider and N. P. Shumway for making the serum of some of these patients available for study.

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LARGE DOSES OF PROPYLTHIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM*

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WITH the introduction of the new antithyroid agents for the treatment of hyperthyroidism, clinicians focused their attention on two main factors: first, the minimal dose required to effect a satisfactory clinical improvement and second, the incidence of undesirable side reactions. The originally suggested dose of propylthiouracil was 75 mg. daily (1), but it was quickly determined by clinical trial that for primary hyperthyroidism 200 to 400 mg. daily of propylthiouracil was required for a satisfactory response (2); and for adenomatous goiter with hyperthyroidism 300 to 500 mg. daily was necessary, the size of the dose depending upon the size of the goiter. A similar experience occurred with Tapazole, since the initially suggested dose of 12 mg. daily was found to be inadequate; the present dose is between 20 and 40 mg. daily. We have been satisfied over the years with this dosage schedule because our results have been satisfactory, even though the response of some patients, particularly those with adenomatous goiter with hyperthyroidism, has been slow.

Experience in treating some 2,000 hyperthyroid patients with propylthiouracil indicated that the incidence of reactions was 1.5 per cent and that the reactions did not seem to be related to the size of the dose, since agranulocytosis occurred in a patient who was receiving a dose of only 50 mg. daily.

The present study of the use of larger doses of antithyroid drugs was suggested by an unsatisfactory experience in 2 patients with severe hyperthyroidism due to adenomatous goiter, who died as a result of the disease despite the use of our routine dose of medication; 1 of these patients (Fig. 1) died after receiving treatment for four and one half months. Since it was thought that perhaps these deaths were caused by failure to administer sufficient drug to reverse the course of the disease, it was decided that a re-

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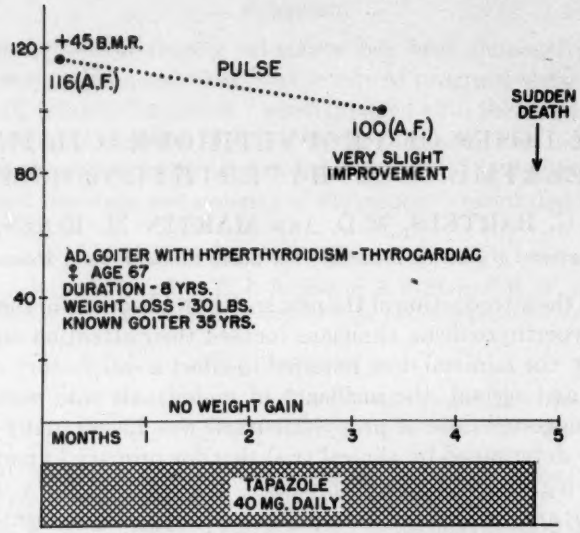

FIG. 1. This elderly patient with severe hyperthyroidism failed to respond to the usual dose of an antithyroid agent and died after receiving treatment for four and a half months.

evaluation of the dosage schedule of the antithyroid agents was necessary in order to determine whether these substances were being utilized to their fullest possible extent. We chose to use propylthiouracil in this study because of its low reaction rate, and avoided Tapazole because our experience with this drug indicated that when the dose was increased over 40 mg. daily, the percentage of reactions increased.

At the beginning of this study it was hoped that a large-dose schedule would be found particularly useful in the depleted thyrocardiac patient with adenomatous goiter, since no medication is available to achieve a rapid initial response in these patients, such as is accomplished in patients with severe primary hyperthyroidism by the use of iodine during the first week of therapy (a procedure commonly used).

There has been very little previous experience with the administration of really large doses of propylthiouracil for the treatment of hyperthyroidism. McCullagh (3) and other investigators, in early studies to determine the minimal effective dose, noted that the rate of fall of the basal metabolic rate paralleled the size of the dose—500 mg. daily being the maximal dose used. They noted no increase in undesirable side effects with the higher dose. Irwin *et al.* (4) reported that 300 to 800 mg. of propylthiouracil daily was necessary, depending on the size of the gland, and that many of their

patients required 500 to 800 mg. daily to control their symptoms; even at this dosage level, some failed to reach a euthyroid state. They speculated that if daily doses of 1,000 mg. were tolerated, there would probably be a more desirable response in resistant cases, but they did not give such a large dose. Bowen and Lenzner (5) used doses of 600 to 800 mg. of propylthiouracil daily for patients with hyperthyroidism complicated by diabetes. They reported that in only 4 out of 41 patients was there unsatisfactory control. One of the 4 patients, during administration of more than 600 mg. daily, had transitory granulocytopenia and 1 had urticaria.

ANALYSIS OF CASES

This report comprises a study of 24 patients with hyperthyroidism, 12 having primary hyperthyroidism and 12, adenomatous goiters with hyperthyroidism. All of the patients selected for this study had hyperthyroidism in severe form; 8 patients had thyrocardiac disease. In all these cases it was thought desirable that a euthyroid state be induced as rapidly as possible because of the high degree of physical depletion.

The patients in this series received propylthiouracil daily in a range between 600 and 1,000 mg. In many cases medication was started with a smaller dose, but this was found to be inadequate to produce a rapid amelioration of symptoms, and hence the dose was increased to the maximum. When patients who were started on large doses reached a euthyroid state in preparation for definitive treatment (surgery or therapy with I^{131}) a smaller dose was given. Eighteen patients had thyroidectomy; those with primary hyperthyroidism received additional Lugol's solution for two to three weeks before operation. Three patients with primary hyperthyroidism received radioactive iodine and 3 patients at the present time are still taking propylthiouracil, awaiting definitive therapy. Eleven patients received a dose of 1,000 mg. daily for periods ranging from five to sixty-four days, 1 patient with a large adenomatous goiter received 800 mg. daily for twenty-eight days followed by 600 mg. for ninety-four days, and 12 patients received 600 mg. daily for periods varying between eleven and 111 days.

A comparison was made of the response of patients receiving these higher doses of propylthiouracil with the response, during our previous experience, of patients receiving smaller doses. The factors considered in the comparison included the rapidity of relief of symptoms, gain in weight, reduction in pulse rate, fall of the basal metabolic rate and decrease in the level of serum protein-bound iodine. An attempt was also made to gain an over-all clinical impression as to the rapidity of attaining readiness for a safe thyroidectomy in this group, as compared with those patients who had received smaller doses.

RESULTS

The results of this study tend to agree with those of our previous experience with the use of the antithyroid drugs, in that the response of patients with adenomatous goiters with hyperthyroidism differs substantially from that of patients with primary hyperthyroidism, the former being more resistant to therapy and requiring a longer period of treatment to bring about a satisfactory result. It was our hope at the beginning of this study that in the adenomatous group, high-dosage therapy would find its greatest use. All the patients with adenomatous goiter (Table 1) responded to the higher dosage schedule, and in most cases were thought to respond somewhat more rapidly than in our previous experience, but in no case was there the desired dramatic, rapid alleviation of symptoms.

In 6 of the 12 patients with adenomatous goiter (Cases 1, 2, 3, 7, 8 and 12) the response was more rapid than we had seen with smaller doses, but it was not striking. Four patients (Cases 4, 5, 9 and 10) responded to larger doses after failing to respond to smaller doses. These latter cases were most encouraging, for they confirmed our previous impression that all patients

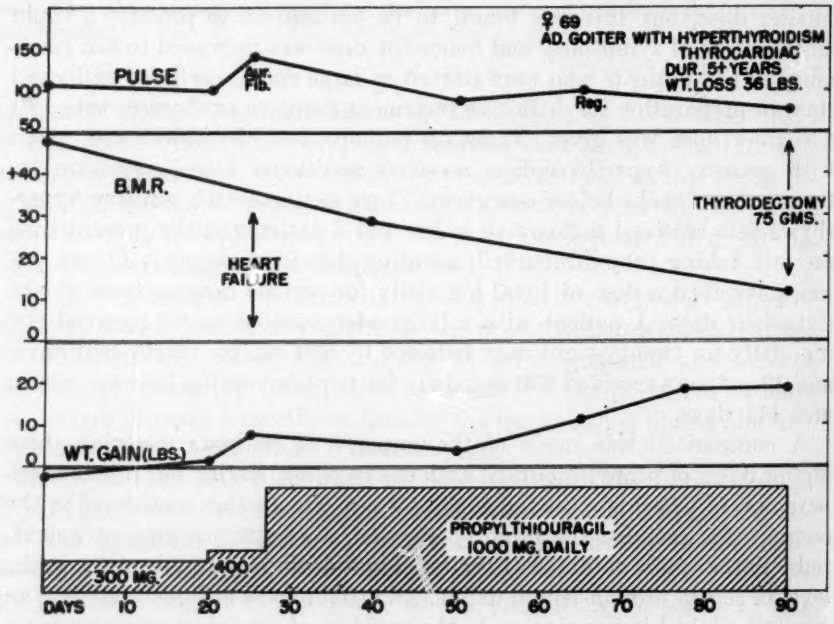

FIG. 2. (Case 10). This patient tolerated large doses of propylthiouracil after previously showing little response to smaller doses. A euthyroid state was induced and thyroidectomy was performed.

with hyperthyroidism will respond favorably to propylthiouracil if the dose administered is sufficiently high and the term of treatment sufficiently prolonged. Figure 2 shows the response to therapy of a patient with adenomatous goiter (Case 10) who, during administration of smaller doses of pro-

TABLE 1. ADENOMATOUS GOITER WITH HYPERTHYROIDISM—TREATMENT WITH PROPYLTHIOURACIL

Case	Age and sex	Duration of symptoms	Weight loss (lbs.)	Preop. BMR (%)	Additional diagnosis and previous treatment	Propylthiouracil dosage		Weight of thyroid (Gm.)	Response
						Mg.	Days		
1	65 F	2 yrs.	50	+49 +23?	Thyrotoxic heart disease	800 600	28 94	165	Slow, steady improvement; operation sooner than expected
2	80 F	1+ yr.	18	+19 +10	Generalized arteriosclerosis	600	103	54	Appeared to improve more rapidly than patients on usual dosage
3	63 F	1 yr.	30	+2 −10	Thyrocardiac; angina, arteriosclerotic heart disease	600 300	63 23	178	More rapid improvement (?)
4	70 F	3 yrs.	72	+60 +10	Thyrocardiac; iodine for 3 yrs; propylthiouracil, 150 mg. for 7 mos.	600 500	33 161	160	Responded slowly to high dosage; no response to previous treatment with iodine and propylthiouracil; weight gain 40 pounds after 244 days
5	55 F	6 mos.	25	+13	Iodine and propylthiouracil for 4–6 mos.	600	111	54	Did well considering iodine-blocked gland; weight gain 20 pounds
6	64 F	5 yrs.; more severe last 3 mos.	40	+55	Thyrocardiac	1,000 300	23		Steady improvement; urticarial skin rash on 49th day; treatment stopped for 10 days; then 300 mg. given with no reaction
7	56 M	8 mos.	35	+30 +12	Diabetes	600 1,000	21 21	236	Steady improvement, possibly more rapid
8	64 F	4 yrs.	45	+28 +14	Thyrocardiac	600	94	245	Improvement of cardiac symptoms; operation sooner than usual
9	53 F	2½ yrs.	40	+54	Thyrocardiac; Tapazole, iodine, propylthiouracil	1,000 400 1,000	9 30 21		Failure to respond to previous treatment; slow but definite response to large doses; still taking drug
10	69 F	5 yrs.	36	+40 +12	Thyrocardiac	300 400 1,000	21 7 64		Poor response to lower doses; gradual improvement on higher doses
11	57 F	3 yrs.	0	+16 +2	Thyrocardiac	600	17	54	Cardiac symptoms improved; diarrhea and fever on 10th day; drug stopped on 17th day and thyroidectomy performed
12	62 F	4 mos.	53	+40 −6	Rheumatoid arthritis	600 300	17 25	63	Good response

pylthiouracil, made little or no progress. Congestive failure actually developed at the end of the fourth week of treatment; however, when the dose was increased to 1,000 mg. daily, a favorable response resulted and the patient was brought to a euthyroid state. She had an uneventful thyroidectomy.

The response of patients with primary hyperthyroidism (Table 2) to high-dosage therapy was in many instances very rapid and dramatic. The 2 patients (Cases 16 and 18) illustrated in Figures 3 and 4, who were severely depleted and on the verge of crisis, responded immediately to the large dose of antithyroid medication; the response was as rapid and perhaps more effective than that following iodine therapy as used heretofore in such critical cases. These 2 examples were typical of the increased response of patients with primary hyperthyroidism to high-dosage therapy. It was noted in 2 other patients (Cases 13 and 17) that the large doses of propylthiouracil overcame the blocking effect of previously given iodine, as there

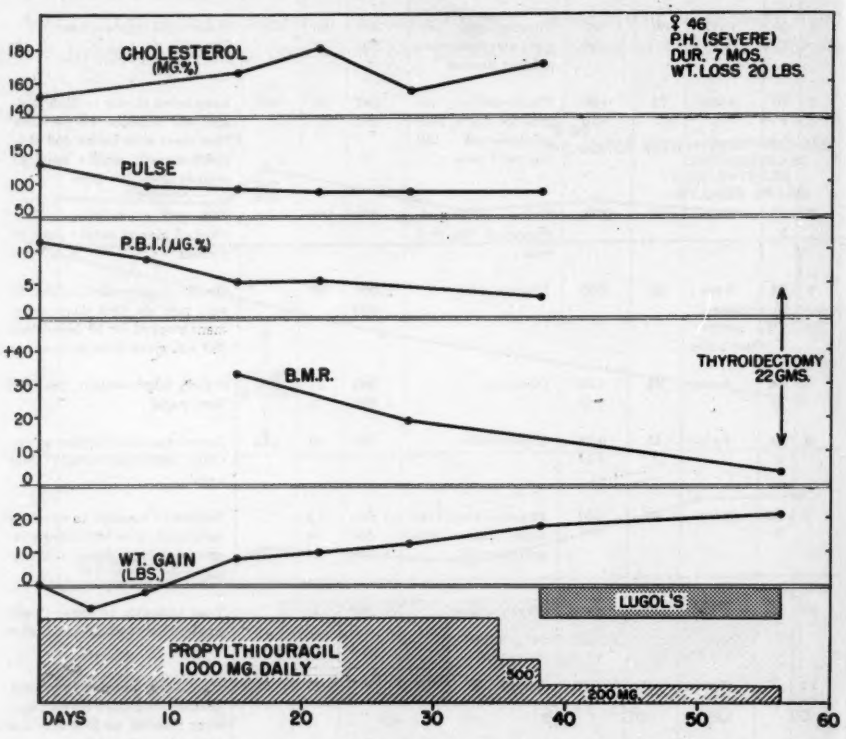

FIG. 3. (Case 16). This patient tolerated large doses of propylthiouracil, and responded rapidly.

TABLE 2. PRIMARY HYPERTHYROIDISM—TREATMENT WITH PROPYLTHIOURACIL

Case	Age and sex	Duration of symptoms	Weight loss (lbs.)	Preop. BMR (%)	Additional diagnosis and previous treatment	Propylthiouracil dosage		Weight of thyroid (Gm.)	Response
						Mg.	Days		
13	59 F	5 yrs.	0	+25 +12	Iodine 2 yrs.	1,000	5	56	Patient was not euthyroid; 5 days of therapy produced full control
14	44 F	2 yrs.	15	+32 (15 days after treatment) +17	Thyrocardiac	600 400 300	11 60 20	37	Patient extremely ill and iodine given with propylthiouracil; thus rapid improvement cannot be attributed to propylthiouracil
15	48 F	15 mos.	50	+37 +4	Thyrocardiac; radioactive iodine 8.2 mg.; Tapazole	600 300	25 19	52	Rapid response with relief of symptoms; weight gain 20 pounds
16	46 F	7 mos.	20	+51 +4		1,000 500 200	35 3 17	22	Rapid response in debilitated patient
17	18 F	1 yr.	8	+46 +10	Iodine	300 600	66 65	67	Little response to lower dose; adequate response to high dose; slow effect due to iodine blocking
18	53 F	8 mos.	35	+39 +3		1,000 200	25 13	78	Rapid, steady improvement; weight gain 12 pounds; operation 1½ months before anticipated
19	61 F	2 yrs.	30	+38		1,000 300	9 20		Rapid response
20	25 F	5 wks.	8	+53 +4		1,000 300 200	33 9 19	28	Rapid response; weight gain 13 pounds
21	73 M	6 mos.	35	+37		600	25		Good response; treated with radioactive iodine
22	61 F	1 yr.	25	+79		300 600	9 38		No response to lower dose; good response to higher dose; radioactive iodine given
23	66 M	3 yrs.	12	+64		1,000	22		Good response; still on treatment; to be given radioactive iodine
24	52 F	1 yr.	43	+53 +16		1,000 600	14 10	45	Responded rapidly and was euthyroid after 14 days; now being prepared for operation

was a more rapid response than had previously been noted in cases of this type. One patient (Case 15) had previously received treatment with radioactive iodine and an unknown dose of Tapazole; these were ineffective, and the severe hyperthyroidism and thyrotoxic heart disease continued. The symptoms were rapidly brought under control, however, by administration of 600 mg. of propylthiouracil daily.

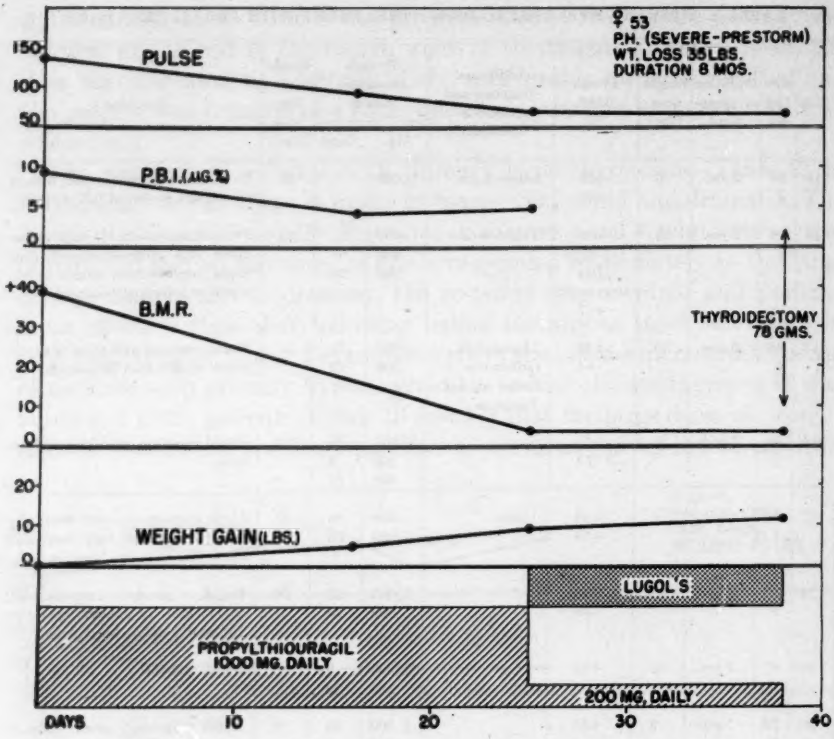

FIG. 4. (Case 18). This patient with very severe hyperthyroidism responded promptly to large doses of propylthiouracil.

As noted in Case 16 (Fig. 3) and Case 18 (Fig. 4), there was a rapid fall in the level of the serum protein-bound iodine. This rapid fall, however, cannot be attributed entirely to the use of high dosage therapy, since Lowenstein (6), Williams (7) and others have reported a similar rapid decline in the concentration of protein-bound iodine in patients given much smaller doses.

In this series there were 2 instances of side effects. In 1 patient with adenomatous goiter a mild urticarial skin rash developed after administration of 1,000 mg. of propylthiouracil for forty-nine days. When the propylthiouracil was discontinued, relief was obtained, and subsequently the drug was again given in a daily dose of 300 mg. without further reaction. In a second patient with adenomatous goiter, diarrhea and fever developed on the tenth day of therapy with 600 mg. of propylthiouracil daily. The symptoms promptly subsided when administration of the drug was stopped on the seventeenth day. This reaction was interpreted as a drug fever. In all

cases, blood studies were made every one to three weeks, but in no case did leukopenia develop. The incidence of undesirable side effects was 8.3 per cent, a higher incidence than occurred with smaller doses. The series is small and a larger number of patients must be treated with large doses of propylthiouracil before an accurate estimation of toxicity can be made. In the light of our present experience, however, the greater risk of untoward reactions with higher dosages is in no way prohibitive, since the reactions observed were not serious.

SUMMARY

Twenty-four patients with hyperthyroidism (primary in 12, and associated with adenomatous goiter in 12) were given propylthiouracil in doses ranging from 600 to 1,000 mg. daily. It was found that doses as high as 1,000 mg. daily could be used with comparative safety, as the incidence of reactions was not prohibitive. There were only 2 reactions in the 24 patients—an incidence of 8.3 per cent; and in neither case was the reaction serious. No instance of adverse effect on the blood cells was noted. Further experience with a large series is necessary, however, to determine the true incidence of reactions, even though it appears that short-term therapy with doses of this size is quite safe.

The response to large-dose therapy in the patients with adenomatous goiter was not striking; but an enhanced response was observed in patients with thyrocardiac disease, and therefore such therapy is particularly indicated in this group. The patients with primary hyperthyroidism showed a dramatic and rapid response to large doses.

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CALCIUM AS A GOITROGEN*

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IN ANCIENT times goiter was thought to be due to the ingestion of some poison in the diet (1), air (2) or water (3), but about a century ago attempts were made to correlate its distribution with geologic formation. We find Boussingault (4) in Colombia in 1831, advancing the theory that an excess of calcium in the drinking water may cause endemic goiter. In 1850 Chatin (5), as a result of extensive iodine determinations in food, water and soil, concluded that a deficiency of environmental iodine was associated with the occurrence of goiter. These two theories—lack of iodine and the presence of various goitrogenic substances—have now abundant experimental and field observations to support them. An excess of iodine in the diet will usually prevent the formation of a goiter in a normal individual, but when the available iodine is at a critical level, then the presence of a goitrogen may tip the scales in favor of thyroid enlargement.

For more than 120 years reports have appeared in the literature of the rôle of calcium as a goitrogen. Notable contributions have been made by McClelland in 1835 and 1859 (6, 7), and in the twentieth century by Berry (8), McCarrison (9), Hellwig (10), Thompson (11) and Buydens (12); but none has shown conclusively the mechanism of action. Among the principal theories advanced have been:

1. Calcium precipitates iodide as an insoluble compound in the gut and thus prevents its utilization (13, 14).

2. Iodine is adsorbed onto, or forms a loose complex with calcium in hard water (12).

3. Dietary calcium in excess causes increased urinary iodide excretion in rats (15).

4. In the presence of a high calcium intake, chloride absorption leads to

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iodide loss (16, 17). The problem is therefore threefold: (a) Is calcium goitrogenic when added to a low-iodine diet? (b) If it is, does calcium produce its effect by preventing absorption of iodide from the gut? (c) If it does not, does the calcium behave like perchlorate in preventing trapping of iodide, like thiourea in preventing binding, or by some other mechanism?

METHODS

Low-iodine diets have been used by many workers to produce simple hyperplastic goiter in rats. Such diets as used for example by Remington (18) and Simpson (19) contain as much as 1 or 2 per cent of calcium carbonate. For this reason the following diet was used:

	Per cent of diet	*Iodine content (γ/100 Gm. diet)*	*Calcium content (mg./100 Gm. diet)*
Ground yellow-maize meal	80.5	8.05	
Bemax	10.0	0.001	
Low-vitamin casein (Genatosan)	6.0	0.60	358 mg.
Sodium chloride	2.0	0.096	
Dried liver (Evans)	0.5	0.011	

It was stored dry and mixed with distilled water to a firm paste before use. Distilled water was freely available in the cages at all times. This diet contains essential vitamins but rats do not thrive as well, nor gain weight as rapidly as those taking the diet with the addition of 2 per cent calcium carbonate.

The rats were given I^{131} in 5-microcurie doses by intraperitoneal, subcutaneous, or stomach-tube injection, according to the requirements of the experiment. Thyroidal radioiodine uptake was measured under light ether anesthesia by placing the rat in a holder, screening the body and head with lead cylinders, and placing the neck area at the center of a "coronet" (Fig. 1) of eight Geiger-Müller tubes connected to a conventional scaler circuit. Counts, each of 1-minute duration, were made at 2-hour intervals. The activity of the alimentary tract was measured by dissecting out the gut from diaphragm to anus, placing it in a glass tube and counting it in the same apparatus. Activity was expressed as a percentage of the administered dose.

Thyroids were dissected and weighed on a torsion balance. They were fixed and paraffin wax sections were cut at 5-micron intervals. Stripping-film autoradiographs were prepared by the method of Pelc (20).

RESULTS

1. *Increase of thyroid weight and I^{131} uptake with calcium*

Two groups of rats were fed on the low-iodine diet, one group having 2 per cent calcium carbonate added. For comparison, a third group received the same diet with the addition of potassium iodide to the drinking water; this provided approximately 2 micrograms of iodine per day, which is assumed to be the normal requirement of a rat. At the end of six weeks the thyroidal radioiodine uptake was measured at 2-hourly intervals. The results are shown in Figure 2. It may be seen that the addition of calcium to the

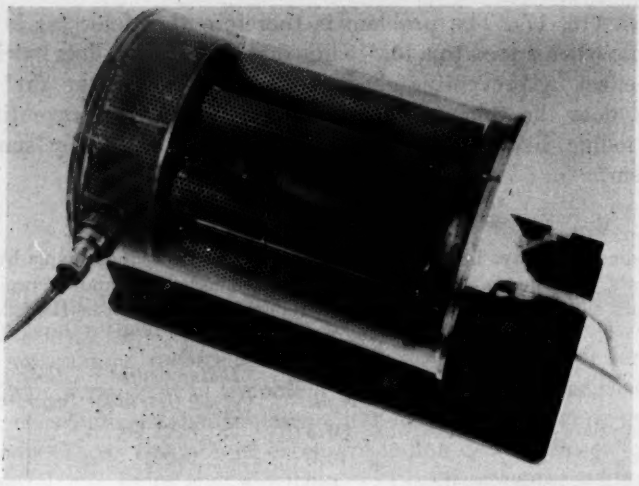

FIG. 1. Eight-tube counter with rat in position. Note cylindrical lead shields.

low-iodine diet greatly enhanced the radioiodine uptake. At this point 30 rats from the low-iodine series were injected with radioiodine, killed at twenty-four hours and the thyroids dissected out and weighed. Table 1 shows that the rats which were on calcium had thyroids significantly

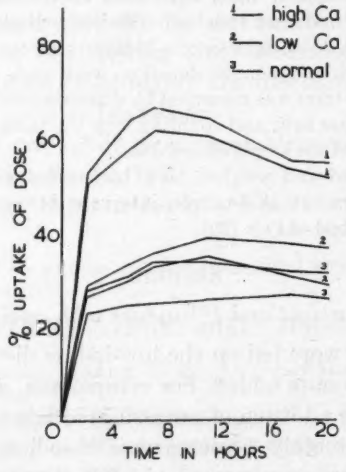

FIG. 2. Graphs of radioiodine uptake measured over the neck area in rats maintained for six weeks on a low-iodine diet, with and without addition of 2 per cent calcium carbonate.

heavier than those of the other rats. In addition, histologic preparations and stripping-film autoradiographs were made. Figures 3 and 4 show examples. They demonstrate depletion of colloid and follicular hyperplasia, to a degree which appears approximately the same in both groups of rats. The autoradiographs show slight blackening, so that binding of iodide to form hormone is not completely in abeyance. The experiment was repeated

TABLE 1. EFFECT OF SIX WEEKS' INGESTION OF LOW-IODINE DIET CONTAINING 2 PER CENT CALCIUM CARBONATE ON THE BODY WEIGHT, THYROID WEIGHT, AND PERCENTAGE OF RADIOIODINE UPTAKE BY THE THYROID

	Body wt., Gm.	Thyroid wt., mg.	% Uptake at 24 hrs.
Low iodine High calcium 17 rats	169±3.3	25.9±1.1	64.6±2.9
Low iodine Low calcium 21 rats	150±1.0	21.2±0.8	46.4±2.5
Added KI 2γ/day 5 rats	200±6.9	21.2±1.5	20.5±1.1

using the subcutaneous instead of the intraperitoneal route for administration of I^{131}, with identical results.

2. *Effect of calcium in diet on absorption of I^{131} from the gut*

The next step was to find out if an excess of calcium in the diet precipitated out the iodide and made it unavailable for absorption. Accordingly, 12 young rats were divided into two groups and a fine rubber catheter was passed down into the stomach of each in turn. Through the tube was run 1.0 ml. of a suspension of the low-iodine diet, 1.0 ml. of water containing 5 μc. of I^{131}, and then a further 1.0 ml. of the suspension. Six of the rats received 2 per cent calcium carbonate in the suspension of the diet. The rats were sacrificed at six hours and placed in the multi-tube counter. Table 2 shows the I^{131} uptake by the two groups to be identical. Presumably radioiodine was neither precipitated nor adsorbed in the calcium carbonate.

In order to discover if the radioiodine were absorbed freely from the gut in the presence of calcium carbonate, even if the latter had been given for a considerable period, the diet was continued for six weeks. There were three groups: low-iodine, low-iodine with 2 per cent calcium carbonate,

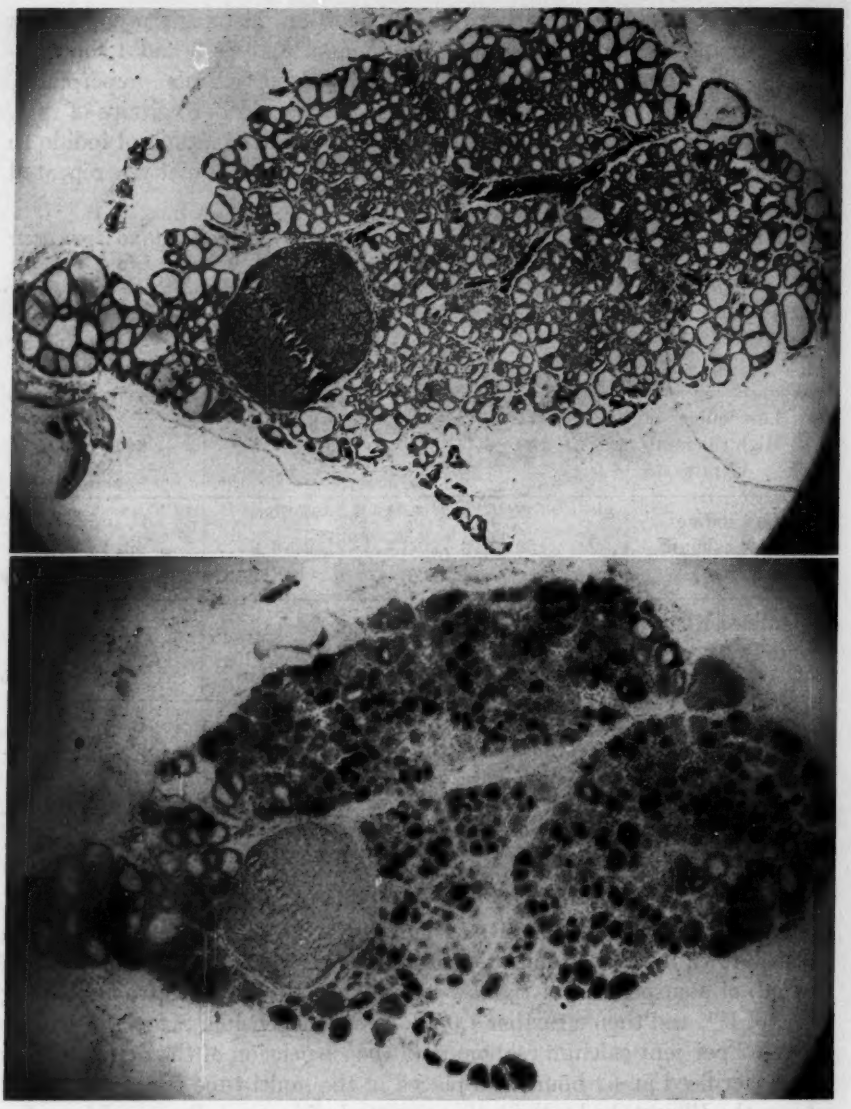

FIG. 3. Histologic section (above) and stripping-film autoradiograph (below) of the thyroid from a rat fed for six weeks on a low-iodine diet plus 2 per cent calcium carbonate. A parathyroid is present.

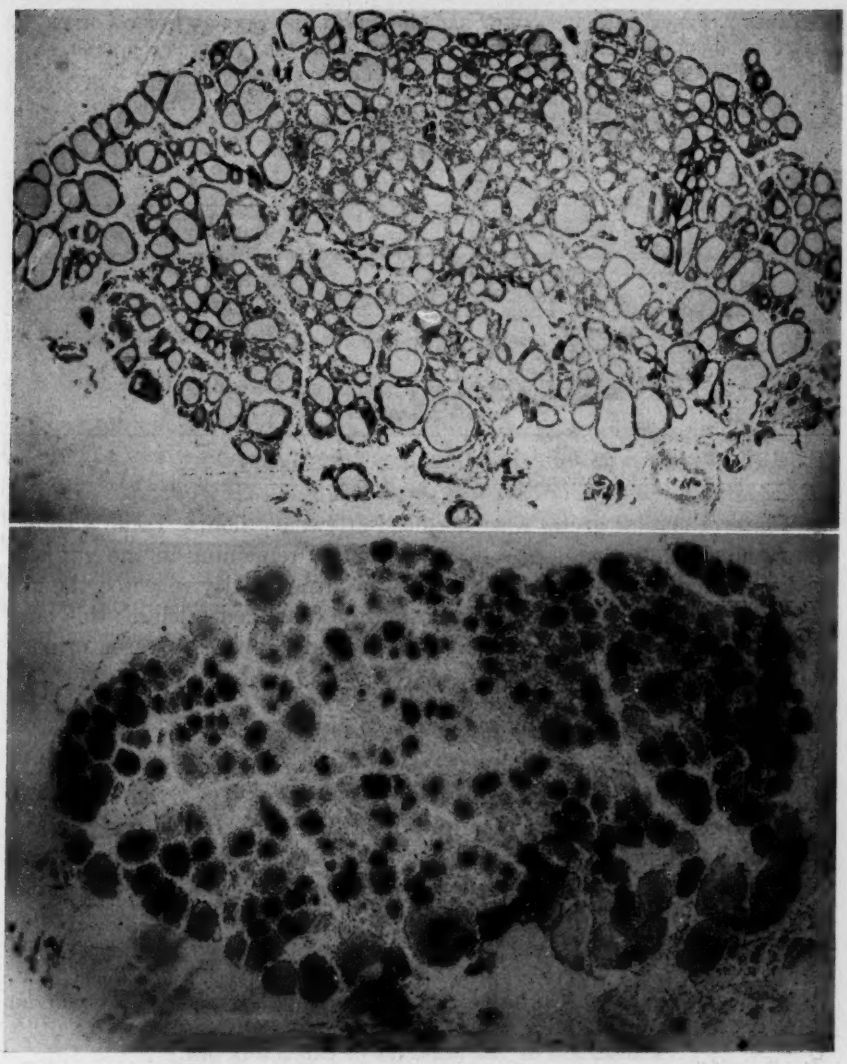

FIG. 4. Histologic section (above) and stripping-film autoradiograph (below) of thyroid from a rat fed for six weeks on a low-iodine diet.

and added iodide. After six weeks they were given by stomach tube a suspension of the diet, radioiodine and a further portion of suspension, then put in metabolic cages for six hours and finally sacrificed. Counts were made of the thyroid, alimentary tract after dissection, and excreta. Two

TABLE 2. PERCENTAGE UPTAKE OF RADIOIODINE BY THE THYROID IN RATS GIVEN 5 MICROCURIES OF I^{131} AND A SUSPENSION OF THEIR DIET BY STOMACH TUBE, WITH AND WITHOUT THE ADDITION OF 2 PER CENT CALCIUM CARBONATE. (NOTE IDENTICAL UPTAKE IN BOTH GROUPS.)

Uptake of radioiodine %	
+ Calcium	No calcium
22.1	22.8
26.2	27.7
26.2	25.6
26.6	29.6
28.4	27.5
	21.9
25.9±1.0	25.9±1.2

days later a similar group was sacrificed at twenty hours. Table 3 shows the results. The amount of radioactive iodine remaining in the gut was negligible in all three groups. The urinary output partly reflected the uptake by the thyroid, being lowest in the rats on added calcium; this may explain Simpson's findings (19) that calcium in the diet increased urinary iodide excretion.

3. *Effect of calcium in diet on rats receiving parenteral iodide*

It was then decided to see if rats maintained on a steady normal intake of iodide showed alteration of thyroid metabolism when given excess calcium carbonate in the diet. The rat requires from 1 to 2 micrograms of iodide daily, therefore these animals were injected subcutaneously twice a week with 7 micrograms of iodide as potassium iodide solution. One group of rats was kept on the low-iodine diet, and the other on the same diet plus 2 per cent calcium carbonate. After five weeks the two groups were in-

TABLE 3. PERCENTAGE OF I^{131} IN DISSECTED ALIMENTARY TRACTS OF RATS AFTER GIVING TRACER DOSE BY STOMACH TUBE. (NOTE THAT MINIMAL AMOUNTS REMAIN, REGARDLESS OF THE PRESENCE OF CALCIUM IN GUT.)

	% I^{131} in gut at		
	6 hrs.	20 hrs.	21 hrs.
+ calcium	2.6	1.84± .01	3.8±0.5
No calcium	4.3	2.56±0.7	1.9±0.7
Controls	4.9	2.2	1.7±0.6

TABLE 4. PERCENTAGE UPTAKE OF RADIOIODINE BY THYROID IN RATS ON HIGH AND LOW CALCIUM DIETS MAINTAINED WITH 7 MICROGRAMS OF POTASSIUM IODIDE TWICE WEEKLY BY SUBCUTANEOUS INJECTION

Uptake of RAI (%) after 2γ KI/day for 5 weeks	
+ calcium	No calcium
52.2±9.4	23.6±2.4

jected with radioiodine as before. It may be seen in Table 4 that there was increased uptake by the calcium-fed group.

4. *Comparison of calcium carbonate with other goitrogens*

The problem of elucidating how calcium acts as a goitrogen is more difficult. The increased avidity of the gland for iodide shows that it does not interfere with the trapping mechanism. If it prevents protein binding then the injection of thiocyanate or perchlorate should discharge most of the trapped radioiodine from the thyroid. Figure 5 demonstrates that this happens in part and the results of injection of 50 mg. of sodium thiocyanate at three hours shows that most of the accumulated iodide had not been manufactured into hormone. Note that the calcium intake was not stopped before the test. The upper line represents the calcium-fed rats. The rapid turnover, however, in the latter could explain these findings.

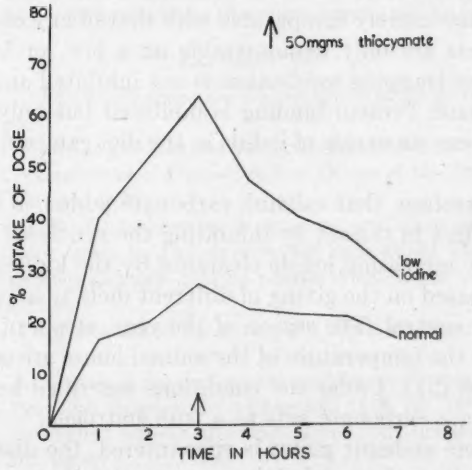

FIG. 5. Effect of 50 mg. of sodium thiocyanate in discharging accumulated radioiodine from the thyroid, in rat maintained on low-iodine diet plus 1 per cent calcium carbonate for 75 days.

On the other hand, the high-calcium diet does not behave entirely like the thiourea compounds, for an excess of iodide in the diet completely prevents the goitrogenic action of calcium. In addition, the autoradiographs show that a little protein binding still proceeds, even in the most hyperplastic of the calcium goiters.

Rats have been maintained on the low-iodide plus 2 per cent calcium carbonate intake for eighteen months. Thyroids weighing as much as 160 mg. have been dissected from the oldest rats.

DISCUSSION

Rats on a low-iodine diet rapidly show depletion of colloid from their thyroids and this is followed by hyperplasia and an increased radioiodine uptake. The addition of 2 per cent calcium carbonate to the diet enhances the effect, producing larger and more hyperplastic thyroids, which have greater avidity for radioiodine.

Radioiodine is absorbed as readily from the gut in the presence of calcium carbonate and the absorption is still unaffected by giving the calcium for many weeks before the radioiodine. Rats maintained on a regular basic iodide intake of 14 micrograms a week injected subcutaneously still show enhanced radioiodine uptake when given added calcium carbonate in the diet. Much of the radioiodine accumulated in these hyperplastic thyroids is rapidly discharged and this discharge can immediately be brought about by an injection of sodium thiocyanate.

The mechanism by which calcium carbonate in the diet acts as a goitrogen is therefore not entirely comparable with that of any of the known goitrogens. Its effects are only demonstrable on a low, or barely sufficient iodide intake. The trapping mechanism is not inhibited and it is therefore not like perchlorate. Protein binding is inhibited but only partially and, unlike the thioureas, an excess of iodide in the diet can completely prevent its action.

It appears, therefore, that calcium carbonate added to the diet, exerts its goitrogenic effect in the rat by inhibiting the synthesis of thyroxine in the thyroid or by increasing iodide clearance by the kidney.

Experiments based on the giving of different diets to animals are notoriously difficult to control. The season of the year, strain of animal, source of foodstuffs and the temperature of the animal house are only some of the possible variables (21). Under the conditions described here, it has been shown that calcium carbonate acts as a true goitrogen.

In regions where endemic goiter is encountered, the distribution of the goiters is difficult to explain and often appears related to certain water supplies (22). The Medical Research Council published a memorandum in 1948 (23) based on a survey in the British Isles of thyroid enlargement,

and the iodine and mineral content of drinking water. It contained a suggestion that the higher incidence of goiter and thyroid enlargement in certain areas of England, as compared with that in certain Scottish areas having waters of similar iodine content, might be attributed to the degree of hardness of these English waters in contrast to the softness of the Scottish waters. The present work offers a partial explanation.

SUMMARY

1. Rats maintained on a low-iodine diet showed hyperplasia of the thyroid, depletion of colloid, increased thyroid weight and increased radioiodine uptake.

2. Addition of 2 per cent calcium carbonate to the diet enhanced all these changes.

3. Absorption of radioiodine from the gut was not inhibited by simultaneous administration of a diet containing calcium carbonate, or as a result of its prolonged administration.

4. Calcium carbonate in the rats' diet was still goitrogenic when the rats were receiving parenteral iodide.

5. The mode of action of calcium carbonate as a goitrogen is discussed.

Acknowledgments

I am particularly grateful to my assistant, Miss Evelyn Poulson, B.Sc., for her skillful and painstaking help. Dr. F. C. Kelly and the staff of the Iodine Educational Bureau have rendered invaluable aid in tracing original papers and making them available to me. Dr. Ruth Allcroft of the Ministry of Agriculture and Fisheries Veterinary Laboratory, Weybridge, kindly arranged for the iodine determinations on the diet.

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DYNAMIC ANALYSIS OF IODINE METABOLISM IN 4 NORMAL SUBJECTS*†

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INTRODUCTION

THE concept of compartment is finding increasing favor in the description of iodine metabolism. Fundamentally, this concept is an attempt to simplify various complex phenomena to a point where logical or mathematical analysis can be applied in a quantitative manner. In general, such types of analysis oversimplify the problem and serve only as a stepping stone to more accurate measurements and more highly refined theory. In many cases the experimental data indicate the validity of a compartment. For instance, the observation that the concentration of a labelled material decreases according to a simple exponential law is strong evidence that the material is present in a single compartment.

Many of the observations in thyroid physiology may be explained on the hypothesis that iodine is present within the body in three identifiable compartments. The first of these represents the inorganic iodide in plasma, extracellular fluid and in the thyroid gland itself. The second represents the organic iodine in the thyroid gland present as monoiodotyrosine, diiodotyrosine, thyroxine or other compounds. The third represents organic iodine in the blood and other extrathyroidal tissues, consisting primarily of thyroxine, although traces of other iodine-containing substances such as triiodothyronine are present. As these substances are known to have different physiologic properties, success with such a simplified model would result only if one substance predominated in each compartment, or if one substance controlled the concentration of the others. Riggs (1) has presented an excellent critical survey of the three-compartment system in

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which is discussed the scope of its validity. Calculations are given for approximate values of the compartment sizes and rate constants, using published data. The concept of the three-compartment system of iodine physiology has been of considerable value in the analysis of data obtained in a group of iodine-deficient subjects (2, 3). Figure 1 illustrates schematically the three-compartment system.

Other experiments validate certain portions of the three-compartment model. The calculation of the thyroid accumulation rate and the extrathyroidal disposal rate of iodide, as described by Myant and Pochin (4) and Keating *et al.* (5), involves the assumption of a single effective iodide com-

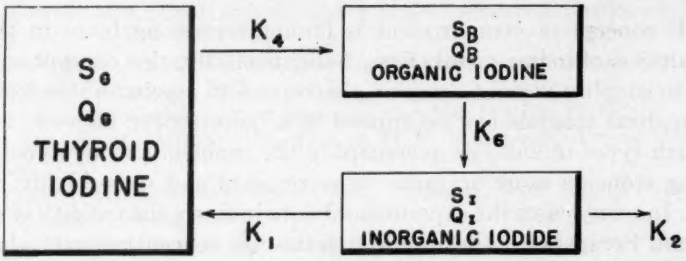

FIG. 1. Assumed three-compartment model of iodine metabolism. Q_I includes iodide present in serum, fluids and thyroid. Q_G includes all organic iodine in the thyroid, and Q_B includes all extrathyroidal organic iodine. The rates of transfer from one compartment to another are indicated. Excretion of organic iodine is neglected.

partment within the body. The simple exponential rate of release of labeled iodine from the thyroid gland in normal patients observed by Burns *et al.* (6), and the biphasic release curves seen in certain hyperthyroid patients (7) and in some iodine-deficient patients (2, 3), provide evidence that iodine within the thyroid gland acts as one compartment. Further, the studies of Myant and Pochin (8) and Albert and Keating (9) indicate that the excretion of radiothyroxine eventually assumes a simple exponential form, indicating that ultimately this material mixes within a single compartment in the body.

The practical analysis of data from even as simple a model as the three-compartment system of iodine metabolism proves to be a formidable task. Various mathematical approaches have been suggested for this purpose (10, 11). However, the application of an electrical analogue to the analysis of data of this type has proved to be useful for the rapid interpretation of experimental data (12). The advantage of the electrical analogue is that alternative models may be rapidly checked and the electrical parameters easily adjusted to give a trial-and-error fit to the observed data.

The object of this investigation is to determine the degree to which the three-compartment model will explain the metabolism of iodine in the normal subject.

EXPERIMENTAL

Four priests of the Dominican Order, members of the Providence College faculty, living a common life, receiving the same diet and engaged in the same type of work, volunteered for the test. They received a physical examination with special care to insure absence of thyroid symptoms. They were instructed to avoid sea food throughout the test period. Table 1

TABLE 1

Subject	Age (yrs.)	Weight (lbs.)	BMR (%)
PC1	32	229	−1
PC2	33	182	−10
PC3	40	195	−1
PC4	48	205	−9

shows the age, weight and basal metabolic rate (BMR) of these 4 subjects. Their ages ranged from 32 to 48 years and their weight from 182 to 229 pounds. The BMR readings were in the range of from ±0 to −10 per cent. Clinical findings in these 4 subjects were entirely negative in any regard which would affect their metabolism of iodine.

The I^{131} was obtained in most cases from the Abbott Laboratory. A 250-μc. sample was diluted to 100 ml. with distilled water, sufficient potassium iodide being added to furnish 10 micrograms of iodide ion per tracer dose. Aliquots were pipetted out in the following quantities: 100 μc. for the dose, 50 μc. for the *in vivo* standard, 2 μc. for the urine standard and 0.1 μc. for each of two serum standards. The dose and the *in vivo* standard aliquots were diluted to 100 ml. in volumetric flasks provided with ground-glass stoppers. The urine standard was diluted to 750 ml. in one of a pair of matched Marinelli beakers. A glass cover was sealed over the top of the beaker with Cenco Sealstix cement. The blood standards were diluted to 4 ml. in standard test tubes and stoppered with rubber stoppers. The dose was checked against the *in vivo* standard before administration. The thyroid content was measured by positioning the patient's neck in contact with a lucite strip rigidly held at a distance of 45 cm. from the face of a Sylvania GG306 high efficiency gamma-ray counter within a special lead shield. The apparatus has been described in a previous report by Burns, Fish, Hackett and Hickey (6). Repeated counts of one-minute duration were taken until a total of 3,000 or more counts was recorded for each counting period. The usual corrections for background and coincidence were applied. The *in vivo* standard was measured with the volumetric flask in contact with the lucite strip previously mentioned. The standard was counted at each thyroid counting period.

Of each urine sample, 750 ml. (or a smaller quantity diluted to this volume) was placed in the second of the matched Marinelli beakers and counted with a counter similar to

that described. A lead shield $\frac{3}{8}$ inch thick completely surrounded the assembled counter and beaker. The urine standard was counted in a similar way, immediately before or after each urine count.

Blood samples were withdrawn either by syringe or Vacutainer, allowed to clot in new test tubes and centrifuged; 4-ml. samples of the serum were pipetted into new test tubes for the I^{131} determination. These determinations were made with a well-scintillation counter which has an efficiency of approximately 10^6 counts per minute (cpm) per microcurie and a background rate of approximately 200 cpm. Thyroid counts were taken at approximately hourly intervals for the first twelve hours after dose administration, several times daily for the next two days, twice daily for the remainder of the first week and daily for the remaining two weeks. Urine samples were collected and assayed fifteen minutes after the dose and at half-hour intervals for the next two hours. Complete collections were made every day for the remainder of the first week and every other day for the remaining two weeks. Care was taken to mix thoroughly all samples.

Blood and urine samples were taken routinely throughout the period for chemical determination. Unfortunately, appreciable errors were detected in the chemical values, originating either from the storage or analysis of the various samples. For this reason, blood and urine samples over a two-day period were taken following the completion of the study. The samples were analyzed in two laboratories and these values were used in the analysis of the data. The reason for this procedure will be discussed later.

RESULTS

The data accumulated for these 4 normal subjects are presented in Tables 2 and 3 and in Figures 2–5. The procedure in plotting specific activity on the figures and the corresponding data in Table 3 will be discussed in the section on analysis. Specific activity is defined as the percentage of the dose of labeled iodine per milligram of iodine in any of its chemical forms.

TABLE 2

Subject	Labeled iodide uptake, U(%)	Labeled iodide excretion, E* (%)	Renal clearance rate, C_K (ml./min.)	Total disposal rate, k_1+k_2 (%/day)
PC1	34.7	64.3	45	8.3
PC2	37.0	61.1	37	12.6
PC3	31.4	67.5	30	7.8
PC4	32.4	66.6	38	9.6
	Net thyroid release rate, k_4' (%/day)	Thyroid retention half-time, T1/2 (day)	Plasma PBI, B(μg./L.)	Iodide excretion, E (μg./day)
PC1	0.65 ± 0.10	106	54	254
PC2	0.74 ± 0.12	93	50	158
PC3	1.27 ± 0.18	55	54	168
PC4	1.12 ± 0.19	62	52	304

TABLE 3

Subject	Iodide compartment, Q_I (μg.)	Thyroid iodine compartment, Q_C (μg.)	Extrathyroidal iodine compartment, Q_B (μg.)
PC1	130	13,500	1,320
PC2	52	7,850	1,400
PC3 (a)	90	4,280	800
PC3 (b)	90	8,300	1,560
PC4	130	8,830	1,530
	Thyroid iodine release rate, $H = k_4 Q_G$, (μg./day)		Urinary iodide excretion rate, $E = k_2 Q_I$, (μg./day)
PC1	135		254
PC2	96		158
PC3 (a)	81		168
PC3 (b)	157		326*
PC4	148		304

* Equilibrium excretion value obtained from analysis.

The thyroidal uptake, U, was determined for the purpose of computation from the urinary excretion of labeled iodide, assuming an appropriate quantity of labeled iodine in the tissues at forty-eight hours. This correction, less than 2 per cent, was obtained by multiplying the concentration of labeled iodine in the serum at forty-eight hours by an estimated volume of distribution. This method was felt to be more accurate than the direct use of the *in vivo* measurements, because of the variable correction for scattering and absorption of radiation in the tissues of the neck. The *in vivo* observations were used for the calculation of the slope of the thyroid retention curve and in the plotting of the thyroid specific-activity curves, S_G, of Figures 2–5. The uptakes for these subjects ranged from 31.4 to 37.0 per cent, corresponding to 48-hour excretions of labeled iodide of 61.1 to 67.5 per cent, all values being well within the normal range for this geographic locale.

The renal clearance rate, C_K, was determined in each of the 4 subjects by measurement of 5 consecutive half-hour urine collections following the administration of the tracer dose, and by measurement of the labeled iodide content of 5 serum samples obtained at the midpoint of the urine collection periods. The renal clearance of iodide ranged from 30 ml./minute in PC3 to 45 ml./minute in PC1. The total disposal rate of iodide from the blood was determined from observations of the amount of labeled iodine accumulated in the thyroid over the first two days in each subject, and

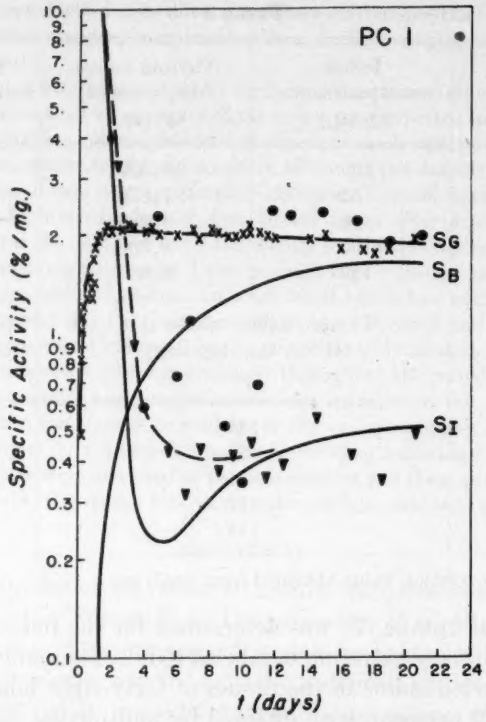

FIG. 2. Specific activity data and computed curves for Subject PC1. The thyroid specific-activity values, S_G, have been plotted by dividing the thyroid labeled-iodine values by the calculated thyroid iodine content. The serum PBI specific-activity values, S_B, are obtained by dividing the serum labeled-PBI values by the observed chemical PBI level. The iodide specific activity is also obtained by simply dividing the two observed quantities, the urinary labeled iodide excretion by the urinary iodide excretion. The solid curves represent the specific activities calculated on the basis of the three-compartment model. The dashed curve indicates the divergence of observed iodide specific activity at early times. For further discussion, see text.

these values ranged from 7.8 per cent/hour for PC3 to 12.6 per cent/hour for PC2. All of these values are well within the normal limits.

The net release rate of labeled iodine from the thyroid, k_4', was determined by a least-squares matching of the *in vivo* data from the second to the twenty-first day to a simple exponential curve, $e^{-k_4't}$. The observed rate, k_4', differs from the true rate of release, k_4, in that a portion of the released labeled iodine is re-utilized by the gland. The net release rates range from 0.65 per cent/day for PC1 to 1.27 per cent/day for PC3, with a stand-

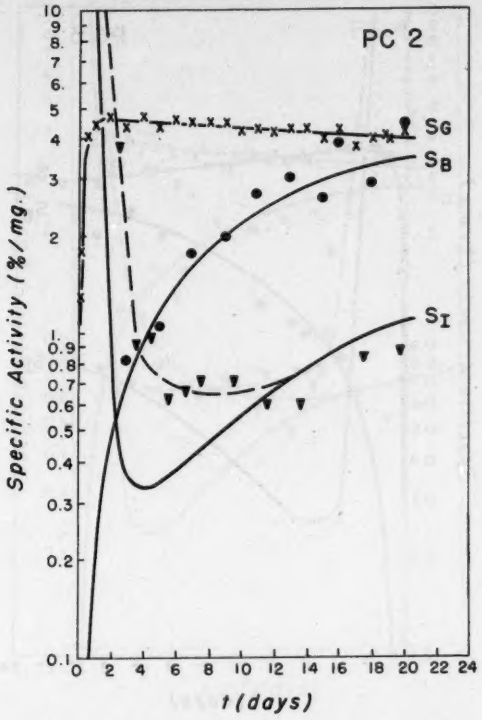

FIG. 3. Specific-activity data and computed curves for Subject PC2. Plotting is the same as in Figure 2.

ard error of about 15 per cent of the calculated value in each case. These values correspond to half-times of retention of labeled iodine in the thyroid of 55 days for PC3 to 106 days for PC1. These values agree with the previous measurements of Burns, Fish *et al.* (6), and are compatible with previous chemical data on the release of hormonal iodine from the gland and of the iodine content of the gland (1).

As mentioned previously, chemical measurements were performed on samples obtained over a two-day interval following the period of labeled iodine observations. Because of the constant diet of these 4 subjects, these samples were undoubtedly representative of the chemical values during the experiment. This is particularly true of the serum protein-bound iodine (PBI) levels, which ranged from 50 μg./liter for PC2 to 54 μg./liter for PC1 and PC3. The urinary excretion of iodide ranged from 158 μg./day for PC2 to 304 μg./day for PC4.

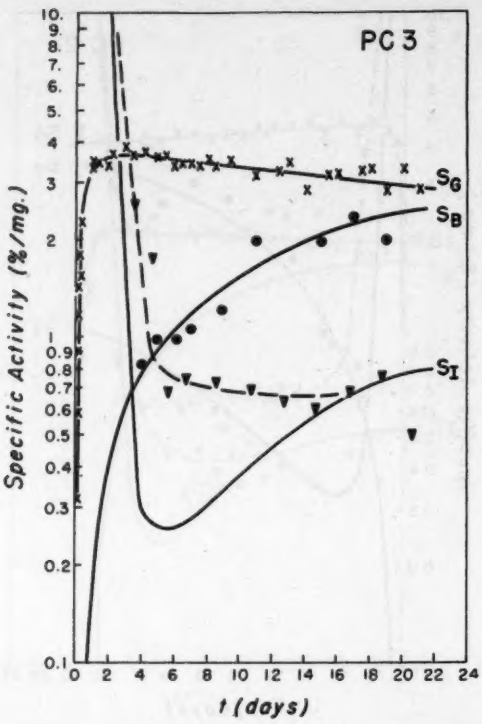

FIG. 4. Specific-activity data and computed curves for Subject PC3. Plotting is the same as in Figure 2, with the exception of iodide data. The observed iodide excretion has not been used, but rather the computed value corresponding to the equilibrium state.

ANALYSIS

In principle, it is possible to analyze the three-compartment model shown in Figure 1 from observations of the time course of the concentration of labeled iodine in the three compartments, and from the chemical determination of one parameter. The most direct and accurate chemical measurement is perhaps the level of protein-bound iodine in the serum, B. From this one chemical observation, the compartment sizes and rates of transfer of iodine from one compartment to another can be determined. In most practical approaches to analysis, the limitation is introduced that the subject be in iodine balance, *i.e.*, that the iodide intake equals the iodide excretion. Further, the possibility is always present that more than one set of values will account for the observed curves. This possibility increases rapidly with the complexity of the model, but in the comparatively simple model of Figure 1, essentially unique values may be obtained.

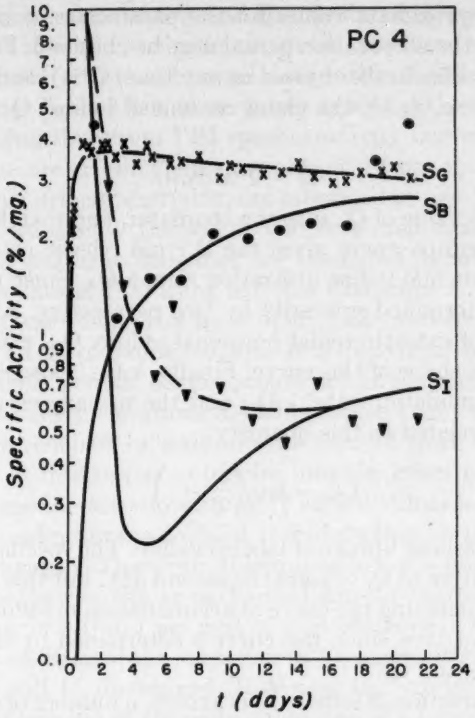

FIG. 5. Specific-activity data and computed curves for Subject PC4. Plotting is the same as in Figure 2.

In the model of Figure 1, three compartment sizes, Q_I, Q_G, and Q_B, and two rates of transfer, k_2Q_I, the urinary excretion of iodide, and k_1Q_I, the rate of entry of iodide into the thyroid, are to be determined in order to perform the complete analysis. The other two rates of transfer, k_4Q_G and k_6Q_B are equal to k_1Q_I in the equilibrium case. Q_I, Q_G and Q_B are defined as the amount of iodine present in any chemical form in each of the three compartments. The corresponding starred values refer to the labeled iodine content in term of per cent of the dose. The analysis will be discussed from the point of view of the use of an analogue computer, but the method would be the same for any mathematical trial-and-error method of curve matching. The curve for serum organic iodine (or PBI) specific activity may be directly plotted, since both the labeled iodine content and iodine content are measured. The ratio of the thyroid gland specific activity, S_G, to that of the blood, S_B, at times beyond two weeks is very insensitive to any of the parameters, and indeed the two specific activities are very nearly equal.

By assuming approximate values for the parameters, a good estimate of S_G at the end of the observation period may be obtained. From the proportion of labeled iodine in the thyroid at any time, $Q^*(t)$, and the specific activity at that time, $S_G(t)$, the gland content of iodine, Q_G, may be determined (1, 3):

$$Q_G = Q^*(t)/S_G(t). \qquad \text{Eq. 1}$$

Introducing this value of Q_G into the computer, and matching the slope of the thyroid retention curve gives the thyroid release rate, k_4Q_G. This is equal to the hormonal iodine utilization rate, k_6Q_B. Since the shape of the curve, S_B, is determined primarily by two parameters, k_6Q_B and Q_B, the total quantity of extrathyroidal hormonal iodine, Q_B, can be determined by matching the shape of this curve. Finally, k_4Q_G is also equal to the thyroid iodide accumulation rate, k_1Q_I; and the urinary excretion of iodide, k_2Q_I, is simply related to this quantity:

$$k_2Q_I = k_1Q_I\left(\frac{1}{U} - 1\right) \qquad \text{Eq. 2}$$

where U is the 48-hour uptake of labeled iodide. The specific activity curves are quite insensitive to Q_I beyond the second day, but this quantity can be determined by matching the curve of accumulation of iodine in the thyroid over the first two days, since this curve is determined by the three parameters, k_1Q_I, k_2Q_I and Q_I.

If the daily excretion of iodide, E, is known, a number of simple, approximate relations may be derived without recourse to the more complicated computational procedures (1, 2, 3). For instance, a simple relationship between the rate of entry of iodide into the thyroid, k_1Q_I, the rate of release from the thyroid, k_4Q_G, and the urinary excretion may be derived.

$$k_1Q_I = k_4Q_G = EU/(1 - U) \qquad \text{Eq. 3}$$

This equation is derived fully in references 1 and 3, and states that for a subject in iodine equilibrium the amount of iodine entering the thyroid equals the amount leaving in unit time and is related to the urinary excretion of iodide by the factor $U/(1-U)$. The net release rate of labeled iodine from the thyroid, k_4', may be obtained directly from a least-squares analysis of the *in vivo* data. From this quantity, an estimate of the amount of iodine in the thyroid, Q_G, may be obtained:

$$Q_G = EU/k_4' \qquad \text{Eq. 4}$$

The determination of Q_B cannot be readily performed by a mathematical method and can most readily be obtained from the computer analysis, although crude estimates may be obtained from the estimated half-time of build-up of labeled hormonal iodine.

It was found that values of k_1Q_I and Q_G calculated by equations 3 and 4, when introduced into the analogue computer, produced specific-activity curves which agreed with the observed data within the observed error for 3 of the 4 subjects. Table 3 lists these values as well as the values of Q_B obtained by matching the serum PBI specific-activity curves, S_B. For PC3, two sets of values are given. The values obtained from equations 3 and 4, using the observed urinary excretion, are tabulated in row (a), whereas the values obtained using only the serum PBI level and analyzing the data entirely with the analogue computer are tabulated in row (b). The discrepancies in the data of PC3 using only the PBI value and using also the observed urinary excretion arise most likely, not from errors of measurement, but from a lack of iodine balance. It is likely that most individuals measured over short periods of time would not be in exact iodine equilibrium. Daily and weekly variations in iodine intake might vary around the average which is required to maintain the thyroid store of iodine at the normal level. It is interesting to inquire into the effect of lack of iodine balance on the specific-activity curves. If an individual in iodine balance suddenly has his iodine intake doubled, it is likely that his thyroidal uptake will remain unchanged. Therefore, the proportion of a dose of labeled iodine entering the thyroid will be unchanged and the thyroid specific-activity will be the same within 1 per cent of that obtained in a similar experiment before the addition of the extra iodide. Consequently, the serum PBI specific-activity will be unchanged. However, the iodide specific-activity will be decreased because of the daily admixture of a larger amount of unlabeled iodide from the diet. Thus, the specific-activity curves cannot be matched by curves computed assuming equilibrium. However, if the analysis is performed using only the serum PBI as outlined previously, the correct values are obtained and the level of urinary iodide excretion is found which corresponds to the equilibrium state. Thus, it is assumed that row (b) gives the correct values for the various parameters and gives the equilibrium level of intake and excretion of labeled iodine for PC3, whereas the excretion over the two-day sample period given in row (a) is less than the equilibrium value, and correspondingly gives incorrect results for the parameters.

An approximate, but useful, relation may be derived from this analysis. If a subject is in equilibrium, the ratio of the specific activity of the urinary iodide to that of the serum PBI at times greater than one week following administration of labeled iodide should equal the uptake, U. If the ratio is smaller than the uptake, the iodide intake is greater than the equilibrium value, and vice versa.

Figures 2 to 5 present the specific-activity data for the iodide, thyroidal iodine, and serum PBI, using the values of Table 3. The three solid curves

on each chart are the specific-activity curves calculated with the computer, again using the parameters of Table 3. In general, the agreement in shape between the computed and observed specific-activity curves is good, considering the number of independently observed variables. The greatest error is introduced in the measurement of the labeled serum PBI, because of the small amount of radioactive iodine present in each sample. Since the labeled serum PBI level was approximately 0.1 per cent/liter, the samples at the end of the three-week period contained approximately 10^{-5} μc. per cc. Furthermore, an analysis of the fluctuations in the data for Subject PC1 indicated that glassware contamination of radioactive iodine was a cause of considerable error with these extremely low-activity samples. Consequently, samples from the following subjects were placed directly into new test tubes after centrifugation and counted for several 20-minute intervals, with frequent background observations. The labeled serum PBI values were considerably improved in these subjects, although still not to the point where small deviations from theory could be detected. It was not feasible to perform a separation of iodide and PBI on these samples. Since the iodide level of the serum is about 10 per cent of the PBI level, and since after the second day the iodide specific-activity is about one-third that of the PBI, samples after two days give the serum PBI specific-activity to within 3 per cent.

The most striking deviation is the behavior of the urinary excretion curve of iodide during the initial time period. Dashed lines have been drawn corresponding to the observed iodide specific activity, and this curve remains clearly higher than the theoretical curve and does not go through the minimum predicted by theory. The most likely explanation is that a small pool of iodide exists within the body, communicating with the main iodide pool with a turnover time of several days. A particularly interesting possibility is that this second iodide pool exists within the thyroid gland itself, as iodide or a compound readily deiodinated is known to be present in this gland and under certain conditions to be secreted directly (3). Further speculation, without direct observation of labeled iodide in the blood and, if possible, within the gland, would be fruitless.

Further refinement in measurement of the serum PBI specific-activity curve could yield considerably more information concerning the exact mechanism of hormone release and breakdown. However, several conclusions may be drawn from the present data. First, there does not appear to be any appreciable delay, *i.e.*, greater than one day, in the release of labeled hormone from the thyroid. Also, the serum PBI curve corresponds to the build-up of a single labeled constituent in the serum. This, of course, does not exclude the presence of other labeled hormones in the serum, but indicates that one component predominates.

A number of quantities may be derived from the data of Tables 2 and 3. Four derived parameters are listed in Table 4. The iodide clearance rate of the thyroid gland may be calculated from the renal iodide clearance and

TABLE 4

Subject	Thyroid iodide clearance rate, C_G (ml./min.)	Serum iodide concentration, (I) (μg./liter)	Iodide space, V_I (liter)	Organic iodine space V_B (liter)
PC1	24.3	3.9	33	24.4
PC2	22.4	3.0	17	28.0
PC3	14.0	3.9	23	28.9
PC4	18.5	5.6	23	29.4

the uptake. The values for these 4 subjects range from 14.0 to 24.3 ml./min. The serum iodide concentration, (I), may be derived from the parameter Q_I, C_K and E, and its range is from 3.0 to 5.6 micrograms/liter. The iodide space, V_I may be derived from the values of Q_I and (I) and values range from 17 to 33 liters. These values yield an average iodide space of 26 per cent of the body weight. The extrathyroidal organic iodine space, V_B, may be calculated from Q_B and H, and values range from 24.4 to 29.4 liters, with an average of 30.4 per cent of the body weight.

CONCLUSIONS

1. The labeled iodine in urine, serum and thyroid and the iodine in urine and serum have been measured over a three-week period on 4 normal subjects.

2. From these data, the quantities of iodine in the thyroid and in the PBI of the serum, and the rate of hormone release, have been calculated.

3. Three of the subjects appeared to be in iodine balance, whereas in the fourth, the value of iodide excretion obtained over a two-day sample period did not agree with the equilibrium value obtained by analysis with an analogue computer.

4. The shapes of the specific-activity curves appear to agree well with those calculated by means of the analogue computer, with the exception of the early portion of the iodide curve. The discrepancy probably results from the presence of a second iodide compartment within the body.

5. The serum PBI specific-activity curve indicates that one labeled compound predominates.

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Teaching Clinic

MYOTONIC DYSTROPHY ASSOCIATED WITH THYROID DISEASE

ENDOCRINE disorders, especially gonadal insufficiency, may occur in association with lenticular opacities and symmetrical atrophy and altered contractility of certain groups of muscles. The syndrome, called myotonic dystrophy, or sometimes myotonia atrophica, is a familial one. The present account is of 2 patients with classic manifestations of myotonic dystrophy. In addition, one had myxedema, and the other had adenocarcinoma of the thyroid gland.

Case I

E.T. (*MGH #614413*) was a 36-year-old single woman of English extraction who was admitted to the hospital for study of diabetes mellitus, myxedema and myotonic dystrophy. Myxedema had been suspected at the age of 15, when she began to complain of fatigue, sleepiness, lethargy, constipation and intolerance to the cold. When given 2 grains of thyroid daily she gained in energy and her fatigue disappeared. For two years preceding admission she was studied in the Out-Patient Department for her thyroid disorder and for diabetes, which had been diagnosed at the age of 33. When desiccated thyroid was withdrawn, her basal metabolic rate fell from −18 to −45 per cent and it was found that only 3 per cent of a tracer dose of radioactive iodine accumulated in the neck in forty-eight hours. An electrocardiogram showed findings consistent with those in myxedema. When thyroid medication was re-instituted there was a prompt rise in metabolic rate to −10 per cent. Shortly before admission, myotonic dystrophy was suspected when she began to complain of weakness of the arms and legs. Muscle atrophy and retarded relaxation of muscles were easily demonstrated. Thyroid medication was again withdrawn ten weeks prior to admission.

Physical examination disclosed a chronically ill, thin, fatigued woman who had marked atrophy of her sterno-cleido-mastoid and anterior neck muscles (Fig. 1). She was unable to flex or extend her head at will. Her forehead was high, but her hair was of normal texture. No thyroid tissue was palpable. She showed the characteristic drooping of the jaw and forward protrusion of the lower lip. There was typical myotonia of the hands, but no evident atrophy of the hands or fingers. The muscles of the arms and legs were atrophic and soft. The ankle, biceps and triceps reflexes were absent. She had a shuffling gait, was unable to raise herself directly from a lying or sitting position, and could not stand on her toes. Slit-lamp examination disclosed a few fleck-like lenticular opacities which were thought to be consistent with myotonic dystrophy.

The laboratory findings are listed in Table 1. The diabetes was moderately unstable but was fairly well controlled with from 10 to 35 units of protamine-zinc-insulin and 5 units of crystalline insulin daily.

It was considered important to test her tolerance to thyroid. Accordingly she was

TABLE 1

	Case I	Case II
Electromyogram	Myotonia	Myotonia
BMR, %	−45, −44, −42	−3
PBI (serum)	0.6 μg./100 ml.	5.0 μg./100 ml.
Thyroidal I^{131} uptake	3%	31.3%
Cholesterol (serum)	387 mg./100 ml.	—
Urinary 17-ketosteroids	3.9 mg./24 hrs.	—
Eosinophils	89/cu.mm.	—
Eosinophils after epinephrine	45/cu.mm.	—
Na (serum)	137 mEq./L.	140 mEq./L.
K (serum)	4.6 mEq./L.	5.3 mEq./L.
Mg (serum)	1.9 mEq./L.	—
Cl (serum)	105 mEq./L.	107 mEq./L.
Calcium (serum)	9.4 mg./100 ml.	—
Phosphorus (serum)	3.0 mg./100 ml.	—
Phosphatase (serum)	1.8 Bodansky units	—
Fasting blood sugar:	275 mg./100 ml.	105 mg./100 ml.
1 hr. after glucose	318 mg./100 ml.	—
3 hrs. after glucose	347 mg./100 ml.	—
Hemoglobin	15 Gm./100 ml.	11.5 Gm./100 ml.
Urine	Glucose +	Normal
X-ray findings in skull	Normal	Normal

discharged from the hospital and the dose was increased at monthly intervals until it reached 1.2 grams daily. At this juncture she was readmitted to the metabolic ward for further study. She was mentally alert but lethargic. Her myotonia was unchanged. She complained as before primarily of fatigue. Basal metabolic rates varied from +11 to +25 per cent. The diabetes proved to be difficult to control because of frequent mild insulin reactions. By all clinical criteria she was euthyroid. The skin was dry, hyperkeratotic in places, and warm. An electrocardiogram eight days before death was normal, with a rate of 96. At 5:30 A.M. on the morning of death the patient apparently had a severe atypical insulin reaction characterized by weakness, left hemiplegia, and respiratory distress. Although the blood sugar was found to be 187 milligrams per 100 ml., she responded dramatically to an intravenous injection of 50 per cent glucose with complete recovery from the hemiplegia. During the day there was mild glycosuria and no additional insulin was given. The blood pressure was stable until late in the afternoon when the patient suddenly expired. There was no acetone in the urine. The final level of serum protein-bound iodine was 12.7 micrograms per 100 ml.

Pathologic examination. There was advanced atrophy of all muscle groups but especially those of the extremities. Nearly all of the fibers of the gastrocnemius had disappeared and those remaining were atrophic. The neck muscles also shared in the prominent atrophy. The viscera were not remarkable except for the thyroid gland, which weighed only 4 grams, was atrophied, and on cut section appeared fibrous. Microscopic sections were unfortunately lost. The heart weighed 185 grams and appeared to have diminished tone. The pancreas showed agonal hemorrhage. The adrenals weighed 5 grams each. There was a 4-cm. cyst in the left ovary and a 1-cm. cyst in the right ovary. The

FIGURE 1

uterus was slightly larger than normal and the endometrium was slightly cystic. The brain showed several small cavities in the anterior-superior border of the globus pallidus on both sides, due presumably to vascular disease with infarction.

Microscopic examination disclosed emphysema of the lungs, and a slightly thinned adrenal cortex with vacuolization in many small focal areas. The lesions in the brain were small cavities surrounded by astrocytic glial tissue. The arteries in this region were calcified. The anterior-horn cells of the spinal cord were little if at all decreased in number, but in this region there was an astrocytic glial reaction. Eight peripheral nerves were microscopically normal. Eleven different muscles showed marked proliferation and central placement of the sarcolemmal nuclei and diminution in the size of muscle fibers. In the more involved fibers, long rows of adjacent nuclei were found within muscle cells. The gastrocnemius muscle was almost completely replaced by fatty and fibrous connective tissue. No cause for death was found.

Case II

L.G. (*MGH #797904*) was a 24-year-old housewife who entered the hospital for thyroidectomy. Nodular growths had appeared in the thyroid gland and both breasts when the patient was 12 or 13 years of age. She underwent thyroidectomies at ages 15, 17 and 21. In addition, at ages 15, 16 and 17, allegedly benign adenomata were removed from the breasts. At the last operation bilateral mastectomy was performed. Pathologic material from these latter procedures was not available for examination. Rounded masses in her neck had recently reappeared. A diagnosis of myotonic dystrophy was made when a striking prolongation of the relaxation phase of hand-grip was observed. She did not complain of muscular symptoms, but on questioning she admitted that for several years she had been aware of difficulty in unclenching her hands. Supernumerary digits had been removed from each hand, and her one child also had supernumerary digits. Her menses were normal. She stated that her father and mother were both well but that one

brother looked just like herself and also had difficulty in unclenching his hands. There were numerous small rounded nodules in the lower neck anteriorly. Complete examination and study was refused at this time.

After considerable urging she returned to the clinic seven months later and entered the hospital. She presented a striking appearance (Fig. 2). The face was long and thin,

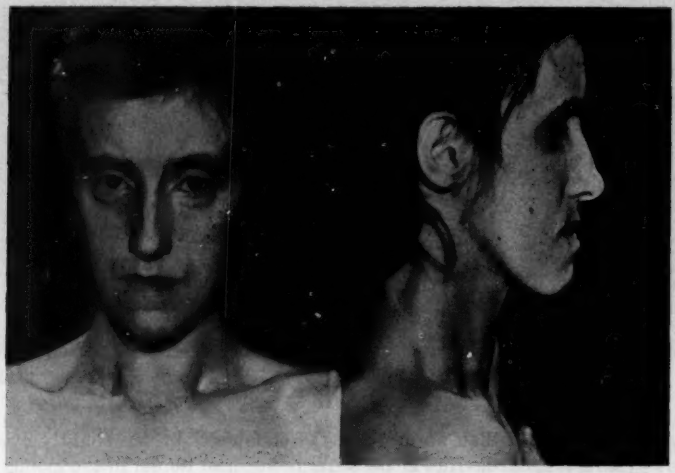

FIGURE 2

tapering to a sagging, pointed jaw. The palate was high and the patient had nasal speech. The eyes showed enophthalmos. The masses in the neck had increased in size in the intervening six months. There was no palpable breast tissue. Reflexes were normal. Myotonia was present in the muscles of the arms, but not in those of the legs. The muscles of the upper extremities were atrophic. Laboratory findings appear in Table 1. She was seen in consultation by an ophthalmologic consultant, who found a mild exposure-keratoconjunctivitis of both eyes and questionable lens opacities. She underwent an uneventful total thyroidectomy. On discharge, she was told to take desiccated thyroid.

Pathologic examination of the removed tissue disclosed well differentiated adenocarcinoma of the thyroid (Fig. 3). The histologic pattern was identical with that of sections from the three previous thyroidectomies.

DISCUSSION

Myotonia is an abnormal property of skeletal muscle characterized by a delay in relaxation. It may be present after voluntary contraction or after mechanical or electrical stimulation. Repeated contractions lead to shortening of the relaxation period, but in severe cases the patient may not be able to "work off" the myotonia completely. Myotonia is improved by heat and brought out or accentuated by exposure to the cold. It is mitigated by alcohol and accentuated by hunger and fatigue and sometimes by psychic factors. Electromyographic recordings of myotonic muscle demon-

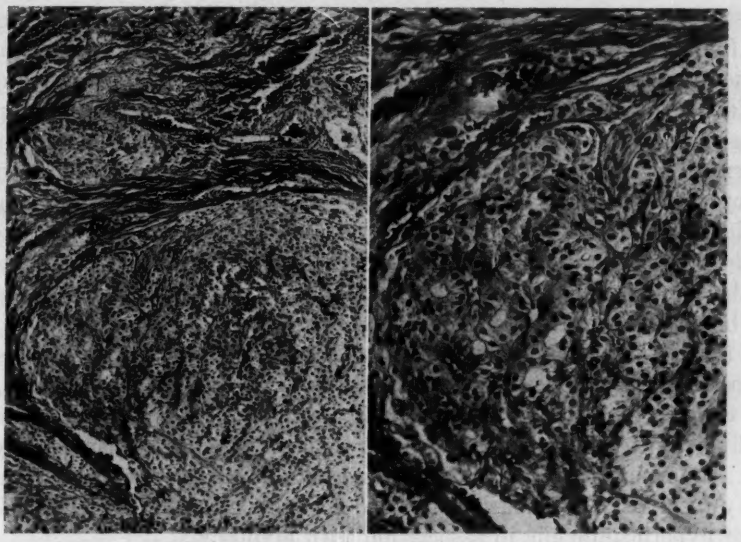

FIG. 3. Low-power and high-power views of adenocarcinoma of the thyroid in Case II.

strate bursts of action potentials when the muscle is at rest, and prolonged electrical activity after cessation of voluntary contraction. Some of these changes are also found in muscles which clinically are not involved in the myotonic process. Electrical myotonia is not abolished by blockade of the nerve supply to the muscle. The fundamental cause of the myotonic phenomenon is unknown. The problem has been thoroughly reviewed by Ravin (1) and by Adams, Denny-Brown and Pearson (2).

There are two distinct disease entities which have myotonia as a characteristic feature. One of these, myotonia congenita, was first clearly described by Thomsen, who himself was a victim of the disorder. It is associated with normal intelligence, normal or hypertrophic musculature, early age at onset, familial incidence, and a normally functioning endocrine system. In contrast, the patient with myotonic dystrophy has a characteristic facies, symmetrical and localized muscle atrophy and oftentimes alterations of one or more of the endocrine organs. Cataracts are often present. Many of these patients are phlegmatic, indolent, and querulous. There is a strong familial incidence. Electrocardiographic changes have been reported (3). The disease first becomes manifest in the second or third decade, or even later. Myotonic dystrophy cannot be distinguished electromyographically from myotonia congenita.

The group of patients with myotonic dystrophy present a kaleidoscopic array of endocrine disturbances. These have been summarized thoroughly by Thomasen (4), by Caughey and Brown (5) and by Waring *et al.* (6). The

most frequently encountered abnormality is gonadal insufficiency. Thomasen found clinical evidence of testicular atrophy in 86 per cent of his 53 male patients. Many of those with hypogonadism have an increased excretion of follicle-stimulating hormone. Histologically the testes show hyalinization of tubules, atrophy of tubular epithelium, and diminished to absent spermatogenesis. The 3 postmortem testes available to Thomasen showed atrophy of the cells of Leydig, whereas the 3 biopsy specimens of Caughey and Brown showed hyperplasia of Leydig cells. The latter finding, together with increased excretion of follicle-stimulating hormone and hyalinization of the tubules constitute a pattern similar to that of the hypogonadism described by Klinefelter, Reifenstein and Albright (7) and by Heller and Nelson (8). Gonadal changes in females are less striking and frequently absent. Thomasen found irregular menses in 64 per cent of his female patients, but the changes are not convincing. Adrenocortical function is not disturbed to a clinically significant degree: neither do signs of adrenal insufficiency occur. Abnormalities of parathyroid function are not encountered. There do not appear to be previously published accounts either of diabetes mellitus or of hyperinsulinemia in association with myotonia.

Patients with myotonic dystrophy customarily have low basal metabolic rates, but myxedema has rarely been observed. The cholesterol content of the blood is characteristically normal. Waring, Ravin and Walker (6) reported several patients with basal metabolic rates of −30 per cent and lower, who appeared to have some of the signs and symptoms of myxedema and who improved on large daily doses of thyroid. One cannot be certain that their patients had true absence of thyroid function. Enlargement of the thyroid has been repeatedly reported in myotonic dystrophy but the precise incidence is unknown, because many of the reported patients have lived in areas of endemic goiter. The pathologic finding in the thyroid has usually been colloid goiter. Six of the 43 adult females in Thomasen's series had detectable enlargements of their thyroids. Histologic examination of 3 of these goiters disclosed distended follicles and cuboidal to flat epithelium. We are aware of no previous report of associated carcinoma of the thyroid. Multiple adenomata of the breasts and polydactylism were also unique features of Case II.

The diagnosis of myotonic dystrophy may often be made on inspection, for the muscle atrophy coupled with the enophthalmos and the receding hair line give these patients an unforgettable appearance. The characteristic change of the eyes is bilateral ptosis with weak closure, a combination seen only in this disease and in myasthenia gravis. The diagnosis is strengthened if cataracts are present and if hypogonadism can be demonstrated. Often enough, other members of the family will be found to exhibit myotonia or cataracts. Of course, myotonia itself is a *sine qua non* of the

diagnosis, which is established by the characteristic electromyographic tracing.

Treatment of myotonic dystrophy is unsatisfactory. The myotonia itself often is of no concern to the patient but, if severe, may be improved by quinine. Cortisone is also said to reduce the myotonic element, without, however, improving the patient generally (9). Associated endocrine disorders may be treated on their own merits. Some benefit may be expected from testosterone replacement therapy in males with hypogonadism. Hypothyroidism, if present, responds to desiccated thyroid, but larger doses than usual may be necessary to restore the euthyroid state, and myotonia is unimproved.

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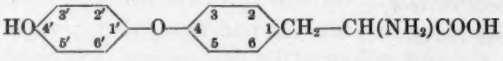
Editorial

METABOLIC EFFECTS OF COMPOUNDS STRUCTURALLY RELATED TO THYROXINE *IN VIVO*: THYRONINE DERIVATIVES

TWENTY-SEVEN years ago Harington proved, by degradation (1) and by synthesis (2) that thyroxine was 3:5-diiodo-4-(3′:5′-diiodo-4′-hydroxy-phenoxy) phenylalanine; the deiodinated compound he named thyronine:



Since that time the physiologic activity of thyronine derivatives has been a matter of considerable interest. In the early years, two methods of assay were mainly used; the first was based on the acceleration of amphibian metamorphosis, the second on the elevation of basal metabolism in small animals (rats and guinea pigs) or in myxedematous patients. Later, a third method became available, which was based on the prevention of goiter resulting from the newly discovered antithyroid drugs. These three methods of assay may, however, reflect different functions of the test compound, and neither the amphibian metamorphosis test nor the goiter prevention test will necessarily give by itself a complete answer in terms of total thyroidal activity; moreover, an important limitation of the amphibian metamorphosis test is its nonspecificity: tadpoles are known to respond to a number of compounds which have virtually no effect on mammalian metabolism; nevertheless, the simplicity of these methods compared with metabolic assays makes them useful for preliminary determinations of activity.

The importance of halogen atoms in the thyronine molecule was demonstrated early by Gaddum (3) and by Abderhalden and Wertheimer (4) in assays of 3:5-diiodothyronine and of thyronine itself—removal of two iodine atoms from the thyroxine molecule resulted in a marked diminution of activity; removal of all four atoms of iodine resulted in a compound totally inactive both in amphibia and in mammals.

Besides thyroxine, one other thryonine derivative occurs naturally, 3:5:3′-triiodothyronine. This compound occurs in the thyroid both as the

free amino-acid and bound in the thyroglobulin molecule, and in blood (5, 6). It possesses high activity in the goiter prevention test and on the growth of thyroidectomized rats (7) as well as in human myxedema (8). Triiodothyronine is metabolically at least as active as is thyroxine: in certain assays it is considerably more active. It has been suggested (7) that triiodothyronine is the active form of the thyroid hormone in tissues, but until the end-target of the hormone is known, this must remain hypothetical. The physiologic significance of triiodothyronine has recently been reviewed in this journal (9) and will not, therefore, be further discussed in the present article. *dl*-Thyroxine has been chosen as the reference compound (unless otherwise stated), since it has been most generally used as such in the work which will be quoted.

Physiologic activity of thyronine derivatives containing halogen atoms other than iodine shows that iodine itself is not essential for activity, though no bromine- or chlorine-substituted thyronine derivative approaches thyroxine in metabolic effect; tetrabromothyronine has about

TABLE 1. ACTIVITY OF THYRONINE DERIVATIVES MODIFIED IN DIPHENYL ETHER RESIDUE, EXPRESSED AS PER CENT OF ACTIVITY OF *dl*-THYROXINE

(Reference numbers in brackets)

Compound	Amphibian metamorphosis	Elevation of metabolic rate of rats, guinea pigs	Myxedema	Goiter prevention
dl-Thyroxine	100 (27)			
l-Thyroxine	200 (27)			
d-Thyroxine			10–20 (29)	
dl-Triiodothyronine	380 (32)			590 (7)
l-Triiodothyronine	840 (27) 300 (33)		high (8)	1000 (7)
3:5-Diiodo-*dl*-thyronine	slight activity (4)	slight activity (30)		1–2 (31)
3′:5′-Diiodo-*dl*-thyronine			inadequately assayed (15)	
dl-Thyronine	0 (3, 4)	0 (30)		0 (14)
dl-Tetrabromothyronine	slight activity (4)		6 (12)	5–10 (11)
dl-Tetrachlorothyronine			0.4 (12)	0.125–0.5 (1)
l-Tetranitrothyronine	slight activity (28) inactive (27)	slight activity (28)		? (28)
3:5 Dibromo-3′:5′-diiodo-*dl*-thyronine	slight activity (4)	10–15 (13)		
3:5-Dichloro-3′:5′-diiodo-*dl*-thyronine		1 (13)		
3:5-Diiodo-3′:5′-dibromo-*dl*-thyronine	high activity (4)	1 (13)		
3:5-Diiodo-3′:5′-dichloro-*dl*-thyronine	high activity (4)	1 (13)		
3′-Fluoro-*dl*-thyronine				0 (14)
3:5-Diiodo-3′-fluoro-*dl*-thyronine				2.5–5 (14)
3:5-Diiodo-3′:5′-difluoro-*dl*-thyronine				1.5–3 (14)
3:5:3′-Triiodo-5′-fluoro-*dl*-thyronine				33 (14)
3:5-Diiodo-3′:5′-dimethyl-*l*-thyronine	280 (27)			
3:5-Diiodo-3′:5′-dimethyl-*dl*-thyronine	160 (27)			
dl-Ortho-thyroxine		2–4 (19)		
dl-Meta-thyroxine		0 (19)		
dl-Thyroxine methyl ether	100 (23)		5.5 (18)	
Sulfur analogue of thyroxine (*dl*)			24 (18)	
2′:6′-Diiodo-*dl*-thyronine			0 (18)	anti-thyroxine activity (14)

TABLE 2. ACTIVITY OF THYRONINE DERIVATIVES MODIFIED IN SIDE-CHAIN EXPRESSED AS PER CENT OF THE ACTIVITY OF *dl*-THYROXINE
(Reference numbers in brackets)

Compound	Amphibian metamorphosis	Elevation of metabolic rate	Myxedema	Goiter prevention
dl-Thyroxine	100 (27)			
n-Acetyl-*dl*-thyroxine	2.5 (24)			30 (24)
n-Acetyl-*l*-thyroxine			20 (18)	
n-Acetyl-*dl*-thyroxyl-glutamic acid			5.5 (18)	
Glycine analogue of thyroxine	35 (24)			0.2 (24)
Benzoic-acid analogue of thyroxine	15 (27), 16 (24)			0.16 (24)
Acetic-acid analogue of thyroxine				100 (26)
Acetic-acid analogue of triiodothyronine		high (26)		100 (26)
Propionic-acid analogue of thyroxine	13,000 (7)			
Propionic-acid analogue of diiodothyronine	80 (27)	1.9 (25)		
Acrylic-acid analogue of thyroxine	290 (25)	2.9 (25)		
Acrylic-acid analogue of diiodothyronine	24 (25)	0.3 (25)		
Hippuric-acid analogue of thyroxine				0.7 (14)
Thyroxamine	100 (4, 23)	active (23), inactive (30)		
3:5 Diiodo-4-(3′:5′-diiodo-4′-hydroxy-phenoxy) aniline	450 (27)			
3:5-Diiodo-4-(4′-hydroxyphenoxy) aniline	16 (27)			
3:5-Diiodo-4-(4′-methoxyphenoxy) aniline	12 (27)			

1/20 of the activity of thyroxine in the goiter prevention test (10, 11) and in human myxedema (12), but tetrachlorothyronine has only about 1/200 of its activity (12).

A number of mixed halogen derivatives of thyronine have also been assayed (4, 13, 14); none of the compounds containing chlorine and iodine has much activity in mammals. Some of the compounds containing bromine and iodine possess considerable activity (13); however, the most active are those containing fluorine and iodine (14). It is perhaps significant that 3:5:3′-triiodo-5′-fluorothyronine, the most potent compound in this series, is closely related in structure to triiodothyronine.

An interesting thyronine derivative has been synthesized by Block and Powell (15), namely, 3′:5′-diiodothyronine. The results of a preliminary assay in a myxedematous patient revealed that the compound had no activity when given in a dose four times as great as an active dose of thyroxine. This compound seems worthy of a more extended assay, in view of the finding (13) that 3:5 dibromo-3′:5′-diiodothyronine possesses considerable metabolic activity in rats—much higher than is found in the thyronine derivative in which the bromine and iodine atoms are transposed (3:5-diiodo-3′:5′-dibromothyronine).

Since the discovery by Woolley that a number of compounds related to diiodotyrosine (16) inhibit thyroxine, the search for antithyroxine compounds has been actively pursued. As many of these compounds only distantly resemble thyroxine, they do not come within the scope of this article,

but one of them should be included: *viz.*, the sulfur (thio-ether) analogue of thyroxine, synthesized by Harington (17) in an attempt to obtain a compound which might possess inhibitory activity on the pituitary without peripheral thyroxine-like activity; this compound was, however, metabolically active, possessing about 12 per cent of the activity of *l*-thyroxine in human myxedema (18).

The *position* of substituents in thyronine molecules exerts a profound influence on their metabolic potency. This is demonstrated by the relative activities of two isomers of thyroxine (19) synthesized by Niemann and his colleagues (20, 21), *meta*-thyroxine and *ortho*-thyroxine (*meta-* and *ortho-* refer to the position of the phenolic group relative to the diphenyl ether linkage). The former compound is inactive in rats in doses of 50 mg./Kg., whereas the latter possesses about 1/25–1/50 of the activity of thyroxine.

2′:6′-Diiodothyronine, synthesized by Niemann and McCosland (22), stands alone as regards physiologic activity, being the only thyronine derivative known at present which has *antithyroxine* activity. Cortell (14) has shown that the simultaneous administration of 2′:6′-diiodothyronine and of thyroxine to thiouracilized rats markedly reduces the antigoitrogenic action of the thyroxine. However, in patients with hyperthyroidism, this antithyroxine action has not been demonstrated; 2′:6′-diiodothyronine had no effect in a patient with Graves' disease (18).

A number of thyronine derivatives in which the phenolic group is blocked have been assayed,[1] but only one of them shows a high degree of activity. The methyl ether of thyroxine, synthesized and assayed by Loesser and Trikojus (23) was found to have an activity in tadpoles almost equal to that of thyroxine; it was also moderately active in patients with myxedema (18).

If we now turn to the question of the activity of the thyronine molecule which has been modified in the side-chain, it is immediately apparent that amphibia are much less affected by such structural alterations than are mammals. For instance, Frieden and Winzler have shown (24) that compared with *dl*-thyroxine, the glycine analogue of thyroxine has an activity of 35 per cent in tadpoles, and 0.2 per cent in mammals; corresponding values for the benzoic-acid analogue are 16 per cent in tadpoles and 0.16 per cent in rats, and for the acrylic-acid analogue (25), 290 per cent in tadpoles and 0.3 per cent in rats. Thyroxamine (4, 23) is almost as effective as thyroxine in accelerating amphibian metamorphosis, but variable findings on its activity in mammals have been reported.

In compounds with acidic side-chains, the potency of the compound is

[1] For a complete list of these compounds, the reader is referred to the papers by Barker *et al.* (25) and Bruice *et al.* (27).

markedly influenced by the length of the chain. Bruice, Winzler and Kharasch (27) have recently found that the propionic-acid analogue of thyroxine is 130 times as active as *dl*-thyroxine in accelerating amphibian metamorphosis; in this test, it is the most potent compound known, and is nearly 90 times as active as the benzoic-acid analogue. As we have already seen, the acrylic-acid analogue is considerably more active than the benzoic-acid analogue in amphibia. The acetic-acid analogue of thyroxine has not been assayed by this method, and cannot therefore be compared with the compounds just discussed; in the goiter prevention assay (26), however, its activity has been shown to equal that of *dl*-thyroxine, so that it far surpasses the benzoic-acid analogue in potency in this assay.

From a lack of evidence, it is not possible to draw any conclusions regarding the relationship between potency and length of side-chain, when the chain contains a basic substituent. However, it may be noted that the ethylamine derivative of thyroxine (thyroxamine) has an activity equal to that of *dl*-thyroxine in amphibia (4, 23), whereas the amine derivative (aniline analogue of thyroxine) has $4\frac{1}{2}$ times this activity (27). It would be interesting to know whether the activity of the methylamine analogue falls between these values.

With regard to structural requirements for thyroxine-like activity, it has been suggested that a halogen or halogen-like substituent must be present in a position *ortho-* to the phenolic group; 3:5-diiodothyronine itself is relatively inactive. However, the assay of a thyronine derivative with a highly dissociated phenolic group has shown that this factor alone is not decisive: tetranitrothyronine has very little activity in tadpoles or in rats (28). Furthermore, a most interesting compound has recently been shown (27) to possess high activity in amphibia: 3:5-diiodo-3′:5′-dimethylthyronine. In this compound, the phenolic group will be less acidic than in 3:5-diiodothyronine, yet it is nearly 3 times as active as thyroxine; whether it is proportionally active in mammals remains to be seen.

A number of substituted thyronine derivatives have been listed in the accompanying tables together with their activities (given numerically where possible), determined by different methods of assay. Scrutiny of these values reveals the large number of compounds which are active in amphibia; it is indeed difficult to discover which of the functional groups in thyroxine must remain to ensure activity. The thyronine skeleton appears to be essential; substituents must be present in both rings, in positions *ortho-* to the phenolic and phenyl-ether groups and some iodine must be present in the molecule, though not necessarily in both rings. The function of the side-chain is a mystery: maybe it is only important insofar as it increases the solubility of the compound in cell constituents and body fluids, thus facilitating its passage into the cell.

A higher specificity is shown in mammals in this respect; the only thyronine derivatives without the alanine side-chain to show high activity are the acetic-acid analogues of thyroxine and triiodothyronine (26); moreover, it appears that some iodine must be present in both rings. If, however, thyronine derivatives such as 3:5-diiodo-3′:5′-dimethyl thyronine and 3:5-diiodo-4-(3′:5′-diiodo-4′-hydroxyphenoxy) aniline, described by Bruice *et al.* (27) are found to be active in mammals as well as in amphibia, current views on the structural requirements for thyroxine-like activity will have to be modified further.

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I wish to express my gratitude to Dr. R. J. Winzler and Dr. N. Kharasch for making their unpublished results available to me.

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Questions and Answers

(Questions submitted at the 1953 Postgraduate Assembly of the Endocrine Society and the University of Minnesota Medical School)

Answers by Irvine McQuarrie, Univ. of Minnesota College of Medicine, Minneapolis, Minn.

QUESTION: Should a high-protein, low-carbohydrate diet be used in idiopathic hypoglycemia?

ANSWER: The high-protein, low-carbohydrate type of diet is most effectual in the type of functional or postprandial hypoglycemia described by Conn (*J.A.M.A.* **134:** 130, 1947). In cases of severe idiopathic infantile hypoglycemia it is not only ineffective but greatly intensifies the tendency to spontaneous hypoglycemic episodes. This appears to be true also in cases of hypoglycemia due to either hypoadrenocorticism or hypopituitarism. Up to the present time, corticotropin (ACTH) has proved to be the most effective therapeutic agent in cases of spontaneous hypoglycemia of undetermined cause in infants and young children (McQuarrie, I.: *A.M.A. Am. J. Dis. Child.* **87:** 399, 1954).

QUESTION: Where does potassium go in an attack of periodic paralysis, if it is not excreted and if there is no increase in the potassium content of the muscles?

ANSWER: Judging from the results of our quantitative metabolic studies on members of a family suffering from hereditary periodic paralysis, the absolute amount of potassium deficit involved in a typical paralytic attack may be too small for accurate determination by ordinary chemical analysis on a biopsy specimen of striated muscle. Such small quantities when distributed throughout the body can be detected by isotopic tracer methods only.

The "metabolic mixture" of the patient at any given moment appears to determine his susceptibility to the attack. For example, when our most highly susceptible patient was maintained on a high-protein, low-carbohydrate, medium-fat type of diet, the total intake of as little as 0.01 Gm. of potassium per Kg. of body weight per day, sufficed to prevent paralytic attacks for many days. A diet excessively high in either carbohydrate or or fat, on the other hand, increased the amount of ingested potassium required to prevent attacks to 0.22 Gm. per Kg. per day. At or near the threshold of an attack, a fraction of a gram of potassium given intravenously or orally is all that is required to prevent the episode. A deficit of similar magnitude can precipitate an attack. Potassium balance studies before, during and after paralytic attacks have failed to show significant abnormalities.

It is tentatively considered that the hypopotassemia associated with a typical attack of periodic paralysis may be explained on the basis of demands for potassium by the enzyme systems involved in intermediary metabolism of fat and carbohydrate.

Answers by George W. Thorn, Peter Bent Brigham Hospital, Boston, Mass

QUESTION: What is the current concept of the etiology of hyperchloremic acidosis associated with tubular insufficiency without glomerular insufficiency?

ANSWER: The syndrome of tubular insufficiency without glomerular insufficiency comprises a chronic state of acidosis, with low plasma pH and CO_2 content and high chloride concentration, accompanied by renal wastage of calcium and potassium and sometimes sodium, in a urine which is persistently alkaline. Blood urea concentration and urea clearance are normal. Calcification of the distal renal tubule is often noted by the pathologist, as well as osteomalacia, sometimes with characteristic pseudo-fractures. An inability of the distal tubules to form an acid urine, with deficient power to synthesize ammonia, has been suggested by Albright as the primary defect. More recently (1), it has been demonstrated in presumably typical cases that massive intravenous infusion of phosphate solutions will provoke production of an acid urine with normal ammonia content. This suggests that inability to reabsorb bicarbonate ion, in the *proximal* tubule, might be the significant abnormality. In this situation, the distal tubule would be presented with an alkaline urine and the stimulus to ammonia production would be lacking.

There has been no evidence presented so far to explain why there should be a renal defect in the first place. A congenital abnormality, sulfonamide damage and chronic pyelonephritis have been suggested, without proof.

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QUESTION: Please discuss the use of testosterone in Addison's disease. What are the indications and dosage?

ANSWER: There have been reports of cases in which testosterone propionate alone or in combination with desoxycorticosterone acetate resulted in striking improvement of female patients with Addison's disease. It is believed by some authors that adrenal androgens play a part in the anabolism of protoplasm, and since the adrenals are the only source of androgens in the female, adrenal insufficiency in these subjects would require androgen treatment. In our experience, when cortisone is used along with DCA in the treatment of patients with Addison's disease, there is little need to add testosterone to the therapeutic regimen.

When adrenocortical insufficiency is associated with hypogonadism, optimum treatment of the patients may require testicular hormone therapy in addition to the treatment with adrenocortical hormones. In these cases, testosterone propionate may be given intramuscularly in a dose of 25 mg. twice weekly. A dose of 300 mg. per month should not be exceeded in females, because of the danger of change in secondary sex characteristics.

QUESTION: How often do you recommend x-ray examination of the chest in patients receiving ACTH and cortisone? What other procedures do you recommend in following such patients?

ANSWER: A routine chest film should be procured on all patients prior to institution of treatment with ACTH or cortisone. The presence of active tuberculosis contraindicates their use, except for substitution therapy with cortisone in Addison's disease. Hormonal therapy may be instituted in patients with inactive lesions, but periodic re-examinations are indicated.

A history suggestive of peptic ulcer necessitates a roentgenologic examination of the upper gastrointestinal tract. The presence of an active ulcer contraindicates ACTH or cortisone therapy. However, such treatment may be carried out in the presence of a healed lesion, provided careful ulcer management is observed. A routine urinalysis for glucose should be performed. Fasting and postprandial blood sugar determinations should

be made in these patients with a family history of diabetes. In the presence of latent or overt diabetes mellitus, periodic blood sugar determinations and urine tests are indicated during hormonal therapy. In patients with hypertension, frequent blood pressure measurements should be made throughout therapy. A low-salt diet and supplementary potassium administration should routinely accompany prolonged treatment with hormones. The body weight should be determined daily, and if weight gain and edema ensue, rigid salt restriction should be instituted. If necessary, diuretic agents should be used. Periodic determinations of the blood potassium, chloride and carbon dioxide content should be performed during therapy, for the detection of hypokaliemic alkalosis. Roentgenologic examination of the spine should be carried out in those patients susceptible to the development of osteoporosis. Periodic psychiatric evaluation is necessary occasionally during hormonal therapy, especially in susceptible individuals.

QUESTION: What has been your experience with desoxycorticosterone trimethylacetate?

ANSWER: Our experience with DCTMA in adrenal insufficiency has been reviewed in *J. Clin. Endocrinol. & Metab.* **13**: 957–973, 1953. Our experience has now been extended to include its use in the maintenance of 75 patients. The additional experience has confirmed our early results. The intramuscular injection of this compound produces effective electrolyte regulation, and control of the body weight, blood pressure, hydration and cardiovascular function. We find that all our patients are effectively controlled on dosages of 25–50 mg. at intervals of three to six weeks. DCTMA, used in conjunction with cortisone orally, represents the optimal treatment of adrenal insufficiency.

The Endocrine Society

THE 1955 ANNUAL MEETING

The Thirty-seventh Annual Meeting of The Endocrine Society will be held in the Chalfonte-Haddon Hall Hotel, Atlantic City, New Jersey, on Thursday, Friday and Saturday, June 2, 3 and 4, 1955.

Dr. Matthew Molitch, 705 Pacific Avenue, Atlantic City, New Jersey, is in charge of the local arrangements for the meeting.

All Scientific Sessions will be held in the Chalfonte-Haddon Hall Hotel. The rooms in which each session will be held will be announced in the program and on the hotel bulletin board. The annual dinner is scheduled for Friday, June 3, at 7:30 p.m., preceded by cocktails at 6:30 p.m.

All members are urged to make hotel reservations immediately, as the hotels expect to be filled to capacity. Correspond directly with Chalfonte-Haddon Hall, advising time of arrival and departure. Make your reservations now and avoid disappointment.

Those wishing to present papers, (time limited to ten minutes) should send four copies of the title and abstract to the Vice-President, Dr. E. B. Astwood, 30 Bennet Street, Boston 11, Massachusetts, not later than *February 1, 1955*. It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and Journals of the Society. The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. Neither footnotes nor acknowledgments to sponsors can be published. References, if used, should be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.
2. The title heading should be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each nonmember-author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of nonmembers who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be given after his name.
   Line 3. Institute of origin and city in which institution is located.

3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter-perfect, as there will be no opportunity for proof reading by authors.
5. Abstracts not conforming to the foregoing regulations will be returned to the authors.

THE 1955 AWARDS AND FELLOWSHIPS

The selection of the recipients of the awards of The Endocrine Society is made by a Committee appointed by the Council of the Society. These awards and fellowships carry no obligation by the recipient to the Society or to the donors.

MEDAL OF THE ENDOCRINE SOCIETY

In 1954 the Council of the Society voted to establish a medal and an honorarium of $1,000 to be given to an individual for work of special distinction in endocrinology. The recipient shall be chosen from nominations presented by members of the Society and is limited to citizens of the United States and Canada.

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishments of an investigator not more than 35 years of age in the field of clinical or preclinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; 1945—Dr. Jane A. Russell; 1946—Dr. Martin M. Hoffman; 1947—Dr. Choh Hao Li; 1948—Dr. Carl Heller; 1949—Dr. George Sayers; 1950—Dr. Oscar M. Hechter; 1951—Dr. Albert Segaloff; 1952—Dr. Seymour Lieberman; 1953—Dr. Sidney Roberts and Dr. Clara Szego (Mrs. Roberts); 1954—Dr. Isadore M. Rosenberg. Prior to 1952 the Award was $1,200. It is now $1,800. If within twenty-four months of the date of the award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

THE AYERST, McKENNA AND HARRISON FELLOWSHIP

This Fellowship was established in 1947. It is designed to assist men or women of exceptional promise in furthering their advancement towards a career in endocrinology. The Fellowship is awarded on alternate years (1955, 1957, etc.) and the stipend, which will not exceed $5,000, may be

divided into two Fellowships in varying amounts in accordance with the qualifications of the appointees. Individuals possessing the M.D. or Ph.D. degree, or candidates for either of these degrees, are eligible for appointment.

Applicants must submit the following information:

1. Evidence of scientific ability as attested by studies completed or in progress.
2. Recommendations from individuals familiar with the candidate and his work.
3. A proposed program of study.
4. Acceptance of the individual by the head of the department in which the Fellowship will be held.
5. A statement that he or she will serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be spent in course work or participation in teaching, the latter purely on a voluntary basis.

THE SCHERING AND THE UPJOHN SCHOLARS OF THE ENDOCRINE SOCIETY

The Council of The Endocrine Society has established a category of Scholars. These grants have been made available through the generosity of the Schering Corporation and the Upjohn Company, and will be awarded to established investigators and teachers in the field of endocrinology who wish to extend their opportunities for work either in this country or abroad.

The awards will not exceed $2,500 annually for each individual and will be granted on the basis of proposals submitted by the applicant. Such applications should include the estimated financial needs. The funds may be used for travel, maintenance and other expenses.

Nominations

Nominations for the Medal of The Endocrine Society, the Ciba Award and the Ayerst, McKenna and Harrison Fellowship may be made by any member of The Endocrine Society. They should be submitted on forms which may be obtained from the office of the Secretary, Suite 319, 1200 North Walker Street, Oklahoma City 3, Oklahoma. *Completed nominations should be returned to the Secretary not later than November 1, 1954.*

Proposals for appointments as Scholars of The Endocrine Society should be made in writing by the individual, and addressed to the Secretary of the Society. *They should be submitted by November 1, 1954.* The Awards Committee will meet in November and notice of awards to successful nominees and applicants will be made not later than December 1, 1954.

The American Goiter Association

THE 1955 ANNUAL MEETING

The next annual meeting of the American Goiter Association will be held in Oklahoma City, Oklahoma, at the Skirvin Hotel, April 28, 29 and 30, 1955.

VAN METER PRIZE AWARD FOR 1955

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held in Oklahoma City, Oklahoma, April 28, 29 and 30, 1955, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length, must be presented in English, and a typewritten double-space copy in duplicate sent to the Secretary, John C. McClintock, M.D., 149½ Washington Avenue, Albany, New York, *not later than January 15, 1955.* The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the Annual Transactions of the Association.

AMERICAN GOITER ASSOCIATION AWARD OF MERIT FOR 1955

The American Goiter Association Award of Merit and its honorarium of $1,000.00 is again offered by its anonymous donor for 1955. Brown Dobyns, M.D., received this award in 1954.

The terms of the gift specify that this sum shall be given to a member of the Association, under 45 years of age, who has made the most important contributions to the knowledge and understanding of thyroid disease or the treatment of thyroid disease.

Candidates for this award are to be nominated by members of the Association. When making a nomination complete details of the nominee's present and past positions and training must be submitted. A complete

bibliography of the nominee's publications is required. A full explanation of the reasons for nominating the candidate must be given.

The candidates submitted are to be reviewed by an anonymous committee appointed by the president. The chairman of this committee will present the deliberations and decisions of said committee to the Executive Council in advance of the annual meeting.

The award is to be called The American Goiter Association Award of Merit and it shall be presented at the annual banquet.

Members of the American Goiter Association are requested to send nominations in duplicate to this secretary, making certain the information required by the deed of gift is included. All nominations must be received *not later than February 1, 1955.*

JOHN C. MCCLINTOCK, M.D.
Secretary,
149½ Washington Ave.,
Albany 10, N. Y.

RECIPIENT OF THE VAN METER PRIZE AWARD FOR 1954

Van Meter Prize

The Van Meter Prize for 1954 was awarded to *Dr. Sam Kirkwood* for his essay entitled "Tyrosine Iodinase: An Enzyme Concerned with the Thyroidal and Extra-thyroidal Metabolism of Organically Bound Iodine."

Dr. Kirkwood was born June 14, 1920, in Edmonton, Alberta, Canada. He received the B. S. degree (with Honours) in Chemistry from the University of Alberta in 1942, and the M. S. and Ph.D. degrees in Biochemistry from the University of Wisconsin in 1944 and 1947, respectively. His Army Service was in the Canadian Infantry Corps, 1944–45. He was Research Assistant, U. S. Biological Warfare Station, Camp Detrick, Frederick, Maryland, in 1947; Assistant Research Officer, Canadian National Research Council, Ottawa, 1948–50; Assistant Professor of Biochemistry, McMaster University, Hamilton, Ontario, 1950–53; and Associate Professor of Biochemistry from 1953 to the present.

First Honorable Mention

First Honorable Mention was given to the essay by *Dr. Solomon Berson and Dr. Rosalyn S. Yalow,* entitled "Quantitative Aspects of Iodine Metabolism. The Exchangeable Organic Iodine Pool and the Rates of Thyroidal Secretion, Peripheral Degradation and Fecal Excretion of Endogenously Synthesized Organically Bound Iodine."

Dr. Berson was born in New York City, April 22, 1918. He received the

B. S. degree from City College of New York in 1938, the M.Sc. degree from New York University Graduate School in 1939, and the M. D. degree from New York University College of Medicine in 1945. He was Assistant in Anatomy, New York University College of Dentistry, 1939–41; George Blumenthal Fellow in Anatomy, New York U. Graduate School, 1941–42; Lecturer in Physiology, Hunter College, New York, 1942–45; Intern, Boston City Hospital, 1945–46; United States Army Medical Corps, 1946–48; Resident in Internal Medicine, Veterans Administration Hospital, Bronx, N. Y., 1948–50; Internist, Radioisotope Unit, 1950–52; Assistant Director, Radioisotope Unit, 1952 to the present; Director, Radioisotope Unit, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y., 1953 to the present.

Dr. Yalow was born in New York City, July 19, 1921. She received the A. B. degree from Hunter College, New York, in 1941, and the M. S. and Ph.D. degrees from the University of Illinois, Urbana, Illinois, in 1942 and 1945, respectively. She was Assistant in Physics at the University of Illinois, 1941–43; Instructor, 1944–45; Lecturer at Hunter College, 1946; Physicist in Federal Telecommunications Laboratory, Research and Development Electronics, 1945–46; Attending Physicist and Associate Director, Radioisotope Unit, Veterans Administration Hospital, Bronx, N. Y. 1947 to the present; and Consultant, Radioisotope Unit, Lenox Hill Hospital, New York City, 1952 to the present.

Second Honorable Mention

Second Honorable Mention was given to the essay by *Dr. Ira S. Goldenberg*, with *Drs. Leo Lutwak, Paul J. Rosenbaum and Mark A. Hayes*, entitled "Thyroid-Adrenocortical Metabolic Interrelations."

Dr. Goldenberg was born in Bridgeport, Connecticut, on February 23, 1925. During World War II he served with the Office of Strategic Services. He received the A. B. degree from the University of Michigan in 1947, and the degree of M. D. from Boston University School of Medicine in 1951. He has been a member of the resident surgical staff of Yale University School of Medicine, New Haven, Connecticut, since 1951; and of the Samuel C. Harvey Metabolic Unit, Department of Surgery, since 1952.

RECIPIENT OF THE AWARD OF MERIT FOR 1954

At the 1954 Annual Meeting, the American Goiter Association Award of Merit was presented to *Dr. Brown M. Dobyns*, Associate Professor of Surgery, Western Reserve University Medical School, Cleveland, Ohio.

Dr. Dobyns' contributions have been many. He has demonstrated in animals the relationship between the pituitary gland and exophthalmos, and has separated the exophthalmic factor of the pituitary from the thy-

roid-stimulating hormone. With radioactive iodine, he has studied the differentiation of hyperfunctioning from nonfunctioning tumors of the thyroid. He has made important contributions to our knowledge of the physiology of cancer of the thyroid, and has demonstrated pleomorphism of human cancers of the thyroid by transplanting such tumors to the eye of the guinea pig. By the use of radioisotopes, he has made significant contributions to our knowledge of the intrathyroidal synthesis of thyroid hormone.

RECIPIENTS OF 1954 AWARDS FOR MERITORIOUS SERVICE

At the 1954 Annual Meeting, the American Goiter Association presented certificates for long and meritorious service to:

Allen Graham, M. D., Melrose, Florida

John DeJ. Pemberton, M. D., Mayo Clinic, Rochester, Minn.

BOOKS RECEIVED

American Lecture Series. Charles C Thomas, Publisher, Springfield, Illinois.

Diagnosis and Treatment of the Infertile Female. By FRED A. SIMMONS, M.D., Asst. Surgeon, Massachusetts General Hospital, and Free Hospital for Women, Instructor in Gynecology, Harvard Medical School, Boston, Mass. A Monograph in American Lectures in Endocrinology, edited by WILLARD O. THOMPSON, M.D.; 83 pages; 8 figures; 1954. Price $2.50.

Laboratory Aids in Endocrine Diagnosis. By ROBERTO F. ESCAMILLA, M.D., Assoc. Clinical Professor of Medicine, Univ. of California Medical School, San Francisco, California. A monograph in the Bannerstone Division of American Lectures in Endocrinology, edited by WILLARD O. THOMPSON, M.D.; 142 pages; 21 illustrations (some in color); index of tests for endocrine diseases; 1954.

Physical Aspects of Betatron Therapy. By JOHN S. LAUGHLIN, Assoc. Professor of Biophysics, Cornell Univ. Medical College, Sloan-Kettering Division and Dept. of Physics, Memorial Center for Cancer and Allied Diseases, New York, N. Y. A monograph in American Lectures in Medical Physics, edited by OTTO GLASSER, Ph.D.; 112 pages; 11 tables; 34 figures; 1954.

Antibodies and Embryos. By F. W. ROGERS BRAMBELL, W. A. HEMMINGS and M. HENDERSON, Dept. of Zoology, University College of North Wales, Bangor; 103 pages; 15 tables; 10 figures; 1954. New York, N. Y., John de Graff, Inc. Price $2.25.

Comment traiter les hyperthyroïdies. Par HENRI BRICAIRE, Médecine des Hôpitaux de Paris, avec la collaboration de J. LEPRAT, Chef de Clinique à la Faculté de Médecine; 135 pages; 4 tables; 4 figures; 1954. Paris, Flammarion. 550 fr.

Endocrinologia: Clinica—Diagnostico—Tratamiento. MARIO SCHTEINGART, Ex-Docente de Patologia Médica de la Facultad de Ciencias Médicas de la Universidad Nacional de Buenos Aires, Ex Jefe del Consultario de Endocrinologia en el Hospital Nacional de Clinicas; 960 pages; 179 illustrations; 1954. Buenos Aires, Editorial Bibliográfica Argentina.

Endokrinologische Psychiatrie by Prof. Dr. M. BLEULER, Professor of Psychiatry in Zürich; 498 pages; 30 illustrations; extensive bibliography; 1954. Georg Thieme Verlag, Stuttgart. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y. DM 46.50.

Glandular Physiology and Therapy. Edition 5, completely revised and rewritten. A symposium issued under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association, by thirty-one contributors who are authorities in their special fields; new format; 41 tables; 20 figures; 1954. Philadelphia, J. B. Lippincott Co. Price $10.00.

Isotopic Tracers. A Theoretical and Practical Manual for Biological Students and Research Workers. By G. E. FRANCIS, Reader in Biochemistry, St. Bartholomew's Hospital Medical College, W. MULLIGAN, Senior Lecturer in Biochemistry, Glasgow University Veterinary School, and A. WORMALL, Professor of Biochemistry, St. Bartholomew's Hospital Medical College; 322 pages; 51 figures; tables; 1954. New York, John de Graff, Inc. Price $7.00.

L'Année endocrinologique (sixième année) by M. ALBEAUX-FERNET, L. BELLOT, P. BUGARD, J. DERIBREUX, L. FUNCK-BRENTANO, M. GÉLINET and J. D. ROMANI; 188 pages; 7 figures; 1954. Masson et Cie, Paris. 875 fr.

Standard Values in Nutrition and Metabolism. Edited by ERRETT C. ALBRITTON, Fry Prof. of Physiology, The George Washington University. Prepared under the direction of the Committee on the Handbook of Biological Data, American Institute of Biological Sciences, The National Research Council, Washington, D. C.; December 1953. Wright Air Development Center, Air Research and Development Command, USAF, Wright-Patterson AFB, Ohio, Aero Medical Laboratory, WADC Technical Report 52-301; 391 pages; 160 tables; 1954.